



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 37

Alan R. Katritzky

Advances in

# Heterocyclic Chemistry

Volume 37

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Advances in

# HETEROCYCLIC CHEMISTRY

*Edited by*

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1984



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## Preface

The present volume consists of five chapters.

W. Flitsch and G. Jones provide the first comprehensive review of pyrrolizine chemistry, an area of increasing interest. The chemistry of the arene oxides has been brought up-to-date by G. S. Shirwaiker and M. V. Bhatt. Following the overall treatment of the electrochemistry of heterocycles given by Lund in Volume 36 of this series, J. E. Toomey has now reviewed electrochemical synthesis and modification of pyridines, a subject of great industrial and academic interest.

P. K. Kadaba, B. Stanovnik, and M. Tišler provide the first comprehensive treatment of  $\Delta^2$ -1,2,3-triazoline chemistry, and the volume concludes with a short chapter covering the isomeric  $\Delta^3$ - and  $\Delta^4$ -1,2,3-triazolines by P. K. Kadaba.

The literature is covered through 1982 and into 1983.

ALAN R. KATRITZKY FRS

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# The Chemistry of Pyrrolizines

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*Organisch-Chemisches Institut der Westfälischen-Wilhelms-Universität,  
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GURNOS JONES

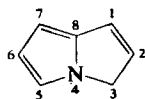
*Chemistry Department, University of Keele,  
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## I. Introduction

Until 1960 the chemistry of pyrrolizines was studied only occasionally. Mosby's compilation<sup>1</sup> includes a few pyrrolizine derivatives, and some structures are questionable.

In the intervening two decades, pyrrolizine research has increased and new synthetic methods have accumulated. In 1964 E. E. Schweizer synthesized the parent compound 3*H*-pyrrolizine (**1**) from 2-formylpyrrole with vinyltriphenylphosphonium bromide.<sup>2</sup> This simple route, suitable for a compound of the instability of 3*H*-pyrrolizine, proved to be a versatile synthetic method.



(1)

The trivial name 3*H*-pyrrolizine has been proposed and widely used instead of the systematic name 3*H*-pyrrolo[1,2-*a*]pyrrole (**1**); the numbering is shown with the formula.<sup>1</sup>

Pyrrolizines have been studied for theoretical reasons. They are intermediates in synthesis and are important natural products. Synthetic studies of the cytostatic mitomycins have aroused further interest.<sup>3-6</sup>

The chemistry of pyrrolizines has previously been reviewed only incidentally in reviews of pyrrolizidine alkaloids.<sup>7</sup> The present review includes pyrrolizine and dihydropyrrolizines as well as their benzo derivatives. Azapyrrolizines, reviewed recently,<sup>8</sup> are only occasionally mentioned. The literature is covered to the end of 1982.

## II. Synthesis

We shall classify synthetic routes according to the number and positions of new bonds formed. Because the sequences of bond formation are not always

<sup>1</sup> W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," Vol. 1, p. 63. Wiley (Interscience), New York, 1963.

<sup>2</sup> E. E. Schweizer and K. K. Light, *J. Am. Chem. Soc.* **86**, 2963 (1964).

<sup>3</sup> T. Kametani and K. Takahashi, *Heterocycles* **9**, 293 (1978).

<sup>4</sup> R. W. Franck, *Fortschr. Chem. Org. Naturst.* **38**, 1 (1979).

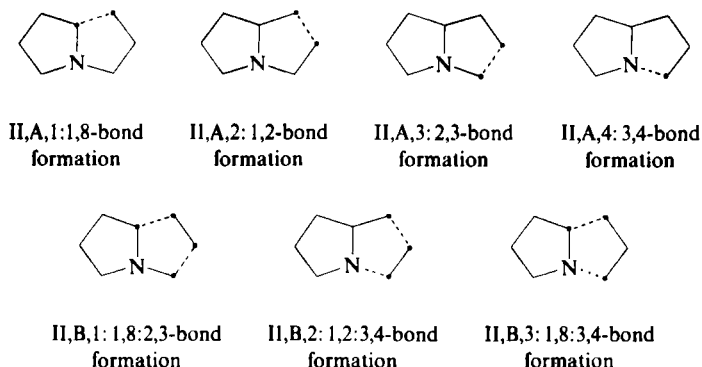
<sup>5</sup> K. Nakano, *Heterocycles* **13**, 373 (1979).

<sup>6</sup> K. Takahashi and T. Kametani, *Heterocycles* **13**, 411 (1979).

<sup>7</sup> D. J. Robins, *Adv. Heterocycl. Chem.* **24**, 247 (1979); *Fortschr. Chem. Org. Naturst.* **41**, 115 (1982).

<sup>8</sup> J. Elguero, R. M. Claramunt, and A. J. H. Summers, *Adv. Heterocycl. Chem.* **22**, 184 (1978).

known, this representation is sometimes arbitrary. The classification used in this article is given in Scheme 1.



SCHEME 1. Classification of pyrrolizine synthesis.

## A. FORMATION OF ONE BOND

### 1. 1,8-Bond Formation

Intramolecular acylation has been used frequently. Houben–Hoesch cyclization of 1- $\beta$ -cyanoethylpyrrole (**2a**) gives 1-oxo-2,3-dihydropyrrolizine (**3a**).<sup>9–17</sup> Difficulties occur because polymerization of the nitrile (**2a**) can be a side reaction. Addition of boron trifluoride [**3a** (33%)]<sup>11</sup> or its ethyl ether complex [**3a** (60–80%)]<sup>15</sup> has been recommended. Treatment of nitrile **2a** with a molten aluminum chloride–potassium chloride–sodium chloride mixture yields 70% of ketone **3a** but the experimental conditions are highly critical.<sup>13</sup> A reproducible procedure that is based mainly on Clemo's specification<sup>9,10</sup> gave 22% of ketone **3a**.<sup>17</sup> Purification of **3a** should be carried out in an efficient fume hood because it appears to induce analgesia.<sup>15</sup>

<sup>9</sup> G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 49 (1931).

<sup>10</sup> G. R. Clemo and A. T. Melrose, *J. Chem. Soc.*, 424 (1942).

<sup>11</sup> J. M. Patterson, J. Brasch, and P. Drenchko, *J. Org. Chem.* **27**, 1652 (1962).

<sup>12</sup> A. D. Josey and E. L. Jenner, *J. Org. Chem.* **27**, 2466 (1962).

<sup>13</sup> J. T. Braunholtz, K. B. Mallion, and F. G. Mann, *J. Chem. Soc.*, 4346 (1962).

<sup>14</sup> V. Carelli, M. Cardellini, and F. Morlacchi, *Ann. Chim. (Rome)* **53**, 309 (1963) [*CA* **59**, 7463e (1963)].

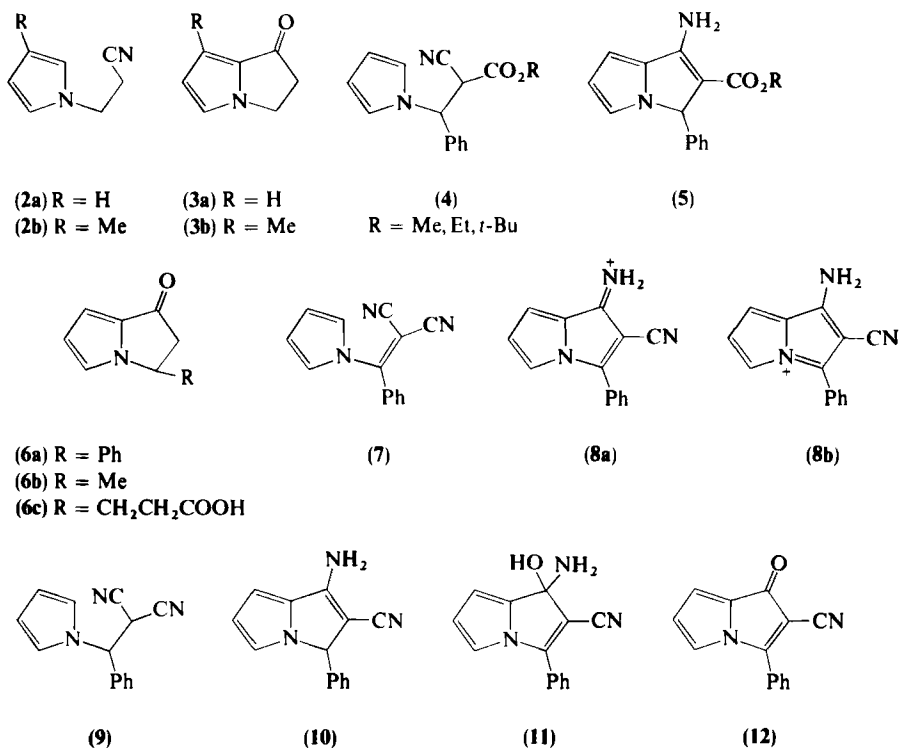
<sup>15</sup> N. W. Gabel, *J. Heterocycl. Chem.* **4**, 627 (1967).

<sup>16</sup> J. Schnekenburger and E. Breit, *Arch. Pharm. (Weinheim, Ger.)* **310**, 152 (1977).

<sup>17</sup> W. Flitsch, J. Koszinowski, and P. Witthacke, *Chem. Ber.* **112**, 2465 (1979).

The 3-methyl group of nitrile **2b** selectively activates C-2 for intramolecular electrophilic substitution so that only one isomer [**3b** (30%)]<sup>18</sup> is formed. Cyclization of nitrile esters **4** in the presence of hydrogen chloride did not lead to the expected ketenimmonium chlorides, 1-amino-3*H*-pyrrolizines (**5**) being formed instead. This may be caused by conjugation of the 1-amino and the 2-alkoxycarbonyl groups on the 1,2-double bond. The dihydropyrrolizinone (**6a**) could be obtained from compound **5** (R = Me)<sup>19</sup> only under drastic conditions.<sup>20</sup>

There is an interesting difference in the cyclization of the closely related pyrrole derivatives **7** and **9**. A reaction of *N*-vinylpyrrole **7** with hydrogen chloride in ether yielded a dark blue immonium salt, represented by resonance structures **8a** and **8b**. The *N*-ethyl analog (**9**), on the other hand, gave the 1-amino-3*H*-pyrrolizine (**10**) under the same conditions. Hydrolysis of **8** did not give the expected pyrrolizinone (**12**) but stopped half way to give adduct **11**.<sup>19</sup>



<sup>18</sup> J. Meinwald and Y. C. Meinwald, *J. Am. Chem. Soc.* **88**, 1305 (1966).

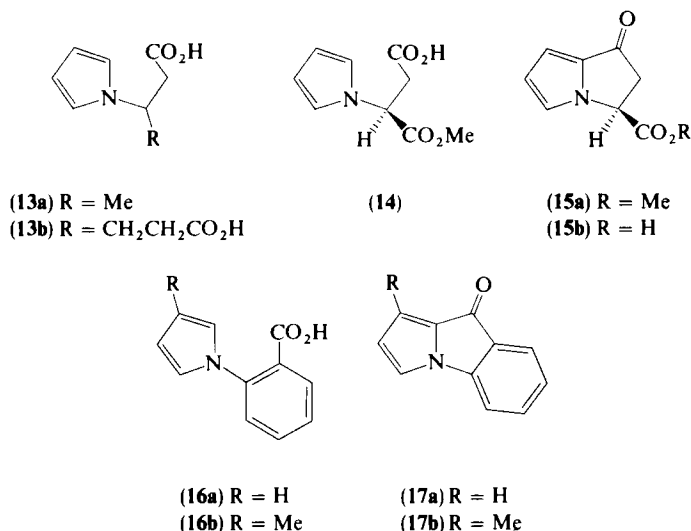
<sup>19</sup> R. Neidlein and G. Jeromin, *Chem. Ber.* **115**, 714 (1982).

<sup>20</sup> R. Neidlein and G. Jeromin, *J. Chem. Res., Synop.*, 232 (1980); *J. Chem. Res., Miniprint*, 3078 (1980).

Intramolecular acylations of pyrrole and indolecarboxylic acids have also been effected. Compound **6b** was obtained from a reaction of  $\beta$ -(1-pyrrolyl)butyric acid (**13a**) using polyphosphoric acid (PPA) as a catalyst. No yield was given but the analogous cyclization of  $\beta$ -(1-pyrrolyl)glutaric acid (**13b**) gave 75% of the pyrrolizinone (**6c**).<sup>12</sup>

A new metabolite from *Streptomyces olivaceus* has been shown to be (2*S*)-1-oxo-2,3-dihydropyrrolizine-3-carboxylic acid (**15b**) by total synthesis. The pyrrolizine ring was formed from the pyrrole (**14**) by stereoselective cyclization with phosphorus pentoxide in toluene in 37% yield. Partial racemization occurred during the hydrolysis of ester **15a**.<sup>21</sup>

The 2-(1-pyrrolyl)benzoic acids (**16**) were converted into benzopyrrolizinones (**17**) using PPA [**17a** (30%)]<sup>12</sup> or phosphorus pentoxide (**17b**).<sup>22</sup> The yield of **17a** could be increased to 90%.<sup>23</sup> Some 2,3-benzopyrrolizin-3-ones bearing substituents in the pyrrole ring and in the benzene ring have been obtained from the corresponding 2-(1-pyrrolyl)benzoic acids by treatment with a mixture of acetic acid and acetic anhydride.<sup>24</sup>



Acid chlorides of acids **16** have been converted to the corresponding benzopyrrolizinones (**17**) in good yield.<sup>25</sup> Malonic acid derivative **18** and

<sup>21</sup> S. J. Box and D. F. Corbett, *Tetrahedron Lett.*, 3293 (1981).

<sup>22</sup> P. Hoechst and E. Röder, *Arch. Pharm. (Weinheim, Ger.)* **308**, 779 (1975).

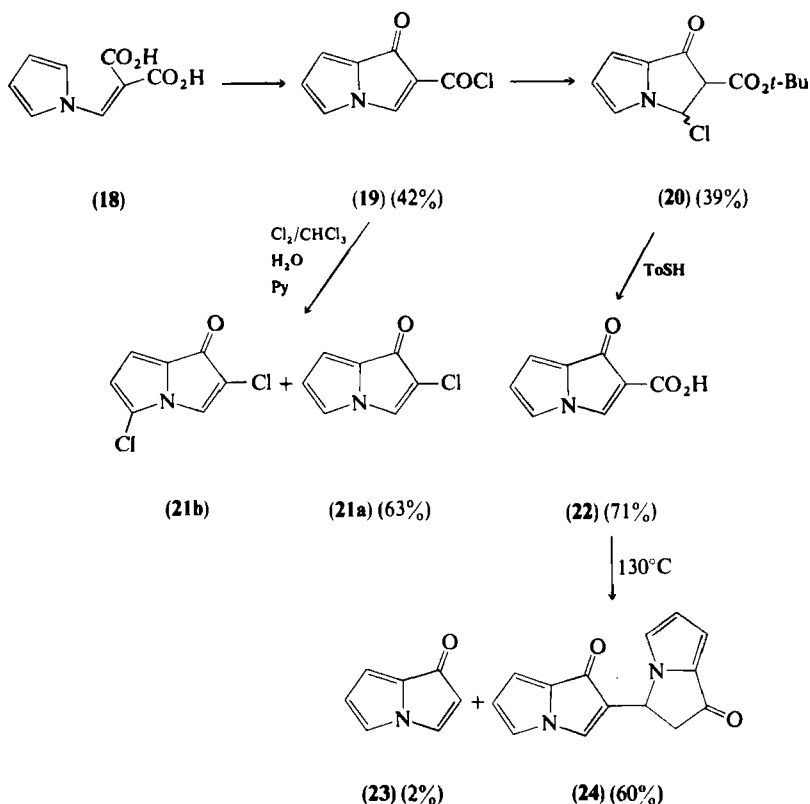
<sup>23</sup> A. S. Bailey, P. W. Scott, and M. H. Vandrevale, *J.C.S. Perkin I*, 97 (1980).

<sup>24</sup> H. Sugihara, N. Matsumoto, and Y. Kawamatsu, *J. Pharm. Soc. Jpn.* **94**, 181 (1974); H. Sugihara, N. Matsumoto, Y. Hamuro, and Y. Kawamatsu, *Arzneim.-Forsch.* **24**, 1560 (1974).

<sup>25</sup> V. J. Mazzola, K. F. Bernady, and R. W. Franck, *J. Org. Chem.* **32**, 486 (1967).



phosphorus pentachloride give pyrrolizin-1-one (**19**) under very mild conditions; it can be transformed into other pyrrolizinones (**20–24**) (Scheme 2)<sup>26</sup>



SCHEME 2

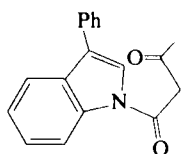
(see also Section III). 3-Phenylindole and diketene gave 1-acetoacetyl-3-phenylindole (**25**), which on treatment with PPA yielded the benzopyrrolizinone (**26**)<sup>27</sup> by electrophilic cyclization.

A convenient route to 1-amino-1*H*-2,3-benzopyrrolizines (**28**) was achieved by a Mannich reaction of aldehyde **27**. Catalytic hydrogenation of either the base (**28a**) or trimethylammonium iodide (**29**) was accompanied by elimination to give compound **30**. Treatment of **29** with potassium cyanide gave nitrile **31**.<sup>28</sup>

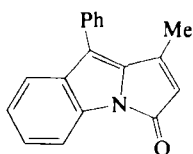
<sup>26</sup> R. Neidlein and G. Jeromin, *Chem. Ber.* **115**, 706 (1982).

<sup>27</sup> E. Röder and U. Franke, *Arch. Pharm. (Weinheim, Ger.)* **309**, 131, 185 (1976); E. Röder, U. Franke, and T. Wirthlin, *ibid.*, 937.

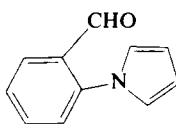
<sup>28</sup> S. Raines, S. Y. Chai, and F. P. Palopoli, *J. Org. Chem.* **36**, 3992 (1971).



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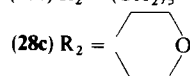
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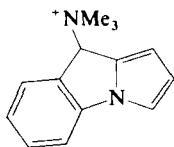


(28a) R = Me

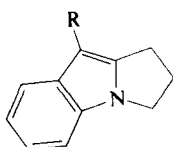
(28b) R<sub>2</sub> = (CH<sub>2</sub>)<sub>5</sub>(28c) R<sub>2</sub> =

Intramolecular condensation of pyrrolidone **32** occurred simultaneously with dehydrohalogenation on treatment with sodium ethoxide, giving the sodium salt, which on acidification yielded the hydroxypyrrolizine (**33**). No information concerning tautomeric structures **33a,b** could be obtained, but a 1,7-dihydroxy-3*H*-pyrrolizine structure (**34**) could be excluded.<sup>29</sup>

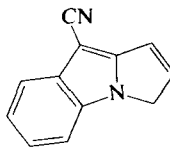
Oxidative coupling of *N*-benzoylpyrroles was achieved with palladium acetate. From a reaction at 110°C in acetic acid, benzopyrrolizinones (**35**) and 2,2'-dimeric compounds (**36**) were obtained. Under the same conditions 1-aryloindoles gave **37** and **38** but no 2,2'-dimeric compounds.<sup>30</sup> Treatment of dibenzoylpyrrolizinones (**37**) with potassium *t*-butoxide/*t*-butyl alcohol containing a small amount of water at 82°C afforded *o*-(2-indolyl)benzoic acids in good yield.<sup>31</sup>



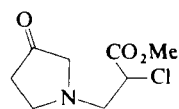
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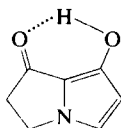
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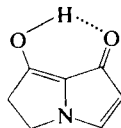
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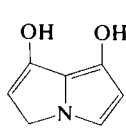
(32)



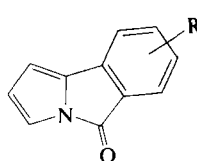
(33a)



(33b)



(34)

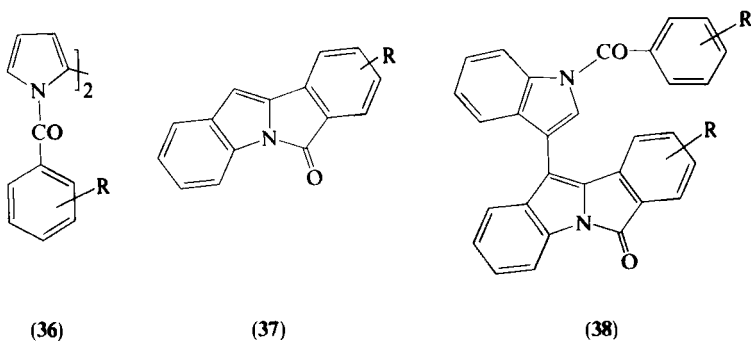


(35)

<sup>29</sup> M. Viscontini and H. Bühler, *Helv. Chim. Acta* **38**, 351 (1970).

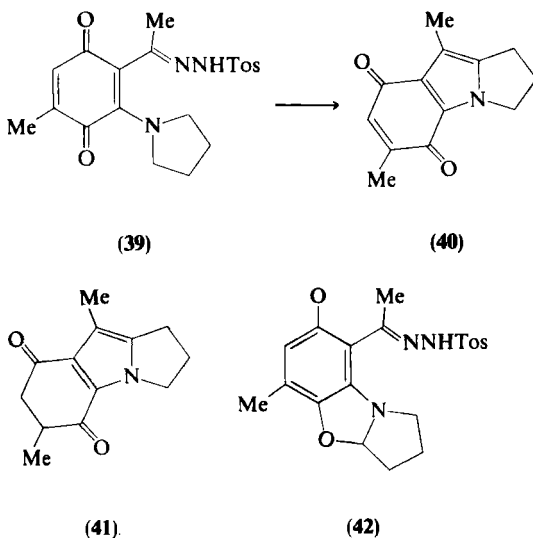
<sup>30</sup> T. Itahara, *Synthesis*, 151 (1979); *Heterocycles* **14**, 100 (1981); *J.C.S. Chem. Commun.*, 254 (1981).

<sup>31</sup> T. Itahara, *Bull. Chem. Soc. Jpn.* **54**, 305 (1981).



A carbene route to benzopyrrolizine derivative **40** with a substitution pattern in the benzene ring similar to that of mitomycins is shown in Scheme 3.<sup>32</sup>

Recently on thermolysis or photolysis of tosylhydrazone **39** a mixture of **40** and **41** was obtained, **42** being a possible intermediate. When **41** was boiled in DMF, **40** was formed; **40** could be reduced by sodium hydrogen sulfite to re-form compound **41**.<sup>33</sup>



SCHEME 3

<sup>32</sup> T. Takada, Y. Kosugi, and M. Akiba, *Tetrahedron Lett.*, 3283 (1974); *Chem. Pharm. Bull.* **24**, 1731 (1976); **25**, 543 (1977).

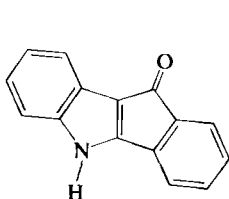
<sup>33</sup> M. Akiba, Y. Kosugi, and T. Takada, *Heterocycles* **6**, 1125 (1977).

Irradiation of 1-acylindoles affords mainly 3-acylindoles.<sup>34</sup> However, 1-(*o*-iodobenzoyl)indole gave 23% yield of the dibenzopyrrolizine **37** (R = H) together with some ketone (**43**).<sup>35</sup>

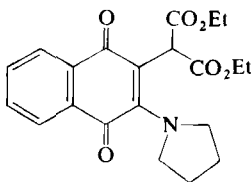
Functionalization of a pyrrolidine  $\alpha$ -position has been observed on photolysis of **44**.<sup>36</sup> Naphthoquinone **46** formed via an oxazoline intermediate (**45**), which is structurally similar to intermediate **42**.

Benzopyrrolizines were obtained from phthalimides by two different photochemical routes. A cyclization of *N*-(2-alkenyl)phthalimides (**47**) with addition of the methanol solvent gave mixtures of benzopyrrolizines (**48**), whose configuration was carefully investigated. Treatment of **48** with hydrochloric acid in chloroform gave pyrrolizines (**49**).<sup>37</sup>

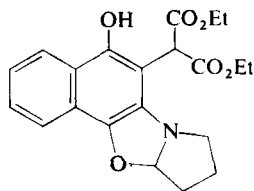
The formation of dibenzopyrrolizines (**51**) on irradiation of *N*-(2-alkylphenyl)phthalimides (**50**) with a high-pressure mercury lamp was reported. Phthalimides containing electron-donating groups resisted cyclization. Hydroxy compounds **51** were dehydrated to dibenzopyrrolizinones by treatment with acids.<sup>38</sup>



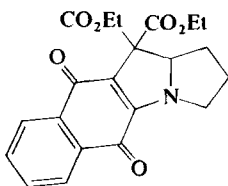
(43)



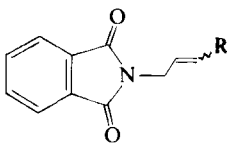
(44)



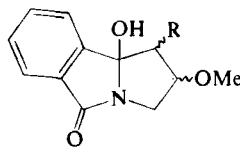
(45)



(46)



(47)



(48)

R = Me, Ph

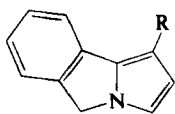
<sup>34</sup> M. Somei and M. Natsume, *Tetrahedron Lett.*, 2451 (1973).

<sup>35</sup> W. Carruthers and N. Evans, *J.C.S. Perkin I*, 1523 (1974).

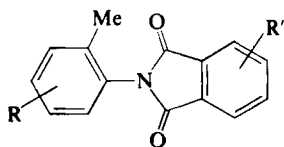
<sup>36</sup> M. Akiba, Y. Kosugi, M. Okuyama, and T. Takada, *Heterocycles* **6**, 1113 (1977).

<sup>37</sup> K. Maruyama and Y. Kubo, *J. Org. Chem.* **46**, 3612 (1981).

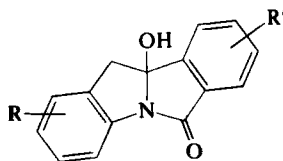
<sup>38</sup> Y. Kanoaka and K. Koyama, *Tetrahedron Lett.*, 4517 (1972); Y. Kanoaka, C. Nagasawa, H. Nakai, Y. Sato, H. Ogiwara, and T. Mizoguchi, *Heterocycles* **3**, 553 (1975).



(49)



(50)

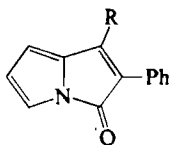


(51)

## 2. 1,2-Bond Formation

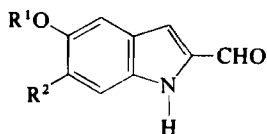
Intramolecular condensation of either 2-formylpyrrole or 2-benzoylpyrrole with phenacyl bromide gave pyrrolizin-3-ones **52a**<sup>39</sup> and **52b**,<sup>40</sup> respectively. *N*-Acylpyrroles presumably are intermediates. Similarly, 5-alkoxy-2-formylindoles (**53**) were converted to benzopyrrolizines (**54**) by treatment with methyl vinyl ketone in the presence of trimethylbenzylammonium hydroxide in dioxane.<sup>41</sup> From diketone **55** a mixture of pyrrolizines [**56a** (25%) and **56b** (11%)] was obtained.<sup>42</sup>

A base-catalyzed cyclization of esters **57** gave a mixture of 3*H*-pyrrolizine esters (**58a** and **58b**).<sup>14,43</sup> The isomers were separated and the dependence of the ratio of isomer **58a** to isomer **58b** on the conditions of cyclization has been investigated.<sup>44</sup> Generally the isomer with the electron-attracting group in the pyrrole ring seems to be the more stable isomer (see Section III).

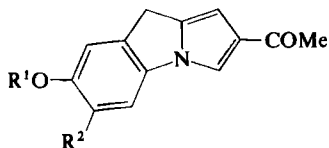


(52a) R = H

(52b) R = Ph



(53)

R<sup>1</sup> = Me, CH<sub>2</sub>PhR<sup>2</sup> = H, Me

(54)

<sup>39</sup> W. Flitsch and U. Neumann, *Chem. Ber.* **104**, 2170 (1971).

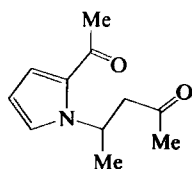
<sup>40</sup> V. Carelli, M. Cardellini, and F. Morlacchi, *Ann. Chim. (Rome)* **51**, 595 (1961) [*CA* **56**, 5911e (1962)].

<sup>41</sup> T. Hirata, Y. Yamada, and M. Matsui, *Tetrahedron Lett.*, 101 (1969); Y. Yamada, H. Takai, K. Hataoka, M. Sakakibara, and M. Matsui, *Agric. Biol. Chem.* **36**, 106 (1972); Y. Yamada, H. Yanagi, and H. Okada, *ibid.* **38**, 381 (1974).

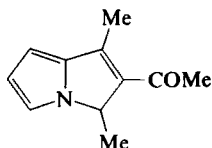
<sup>42</sup> W. Flitsch, F. Kappenberg, and H. Schmitt, *Chem. Ber.* **111**, 2407 (1978).

<sup>43</sup> W. Flitsch, R. Heidhues, *Chem. Ber.* **101**, 3843 (1968).

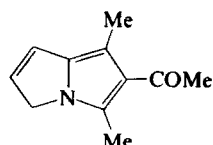
<sup>44</sup> J. Schnakenburger and H. Vollhardt, *Arch. Pharm. (Weinheim, Ger.)* **310**, 186 (1977).



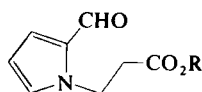
(55)



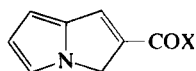
(56a)



(56b)

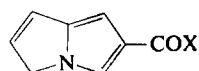


(57) R = Me, Et



(58a) X = OR

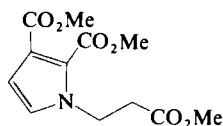
(58b) X = Ph



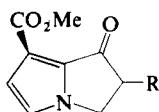
(58c) X = OR

(58d) X = Ph

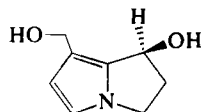
A mixture of the isomeric ketones **58b** (15%) and **58d** (22%) was formed in a reaction of 2-formylpyrrole with  $\beta$ -dimethylaminobenzophenone.<sup>43</sup> Intramolecular Claisen condensation of triester **59** gave ketopyrrolizine **60a**, which, following saponification and decarboxylation to keto ester **60b**, was reduced to give alcohols **61** or **62**. Dihydropyrrolizines such as **61** are metabolites of the highly toxic pyrrolizidines containing dihydroxy derivatives such as **62**.<sup>45</sup> A similar condensation converted ester **63a** to keto ester **64a** (36%), which was subsequently decarboxylated and hydrogenated to the dihydrobenzopyrrolizine (**65**). Similarly, nitrile **63b** gave 85% pyrrolizine **64b**, but attempts to hydrolyze the nitrile led to decomposition. An intramolecular condensation of keto nitrile **66** could not be effected.<sup>23</sup>



(59)

(60a) R = CO<sub>2</sub>Me

(60b) R = H



(61)

Synthetic approaches toward mitomycin analogs have prompted the preparations of many benzopyrrolizines.<sup>46-49</sup> One involved base-catalyzed 1,4-addition of ethyl indole-2-carboxylates (**67**) to an acrylic ester, followed by

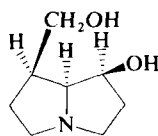
<sup>45</sup> M. Viscontini and G. Gilhof-Schaufelberger, *Helv. Chim. Acta* **57**, 449 (1971).

<sup>46</sup> W. A. Remers, P. N. James, and M. J. Weiss, *J. Org. Chem.* **28**, 1169 (1963).

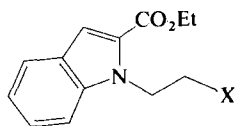
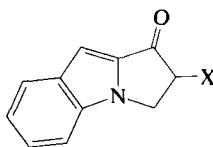
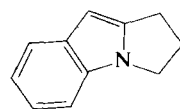
<sup>47</sup> G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.* **86**, 3877 (1964).

<sup>48</sup> G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Org. Chem.* **30**, 2897 (1965).

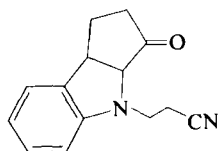
<sup>49</sup> G. R. Allen, Jr. and M. J. Weiss, *J. Heterocycl. Chem.* **7**, 193 (1970).



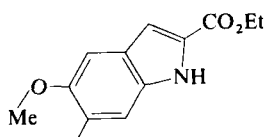
(62)

(63a) X = CO<sub>2</sub>Et  
(63b) X = CN(64a) X = CO<sub>2</sub>Et  
(64b) X = CN

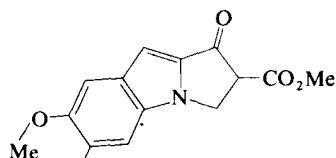
(65)



(66)

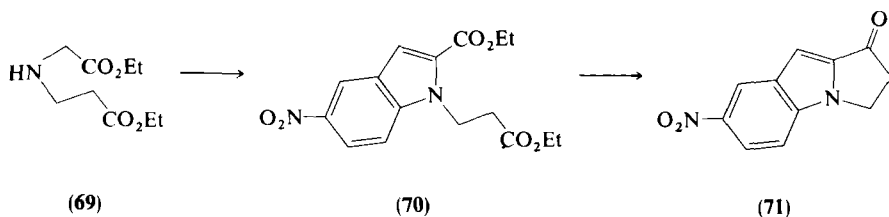


(67)



(68)

a Dieckmann condensation to yield keto ester **68**. The nitrobenzopyrrolizine (**71**) was prepared from 2-chloro-5-nitrobenzaldehyde, which on heating with *N*-ethoxycarbonylmethyl- $\beta$ -aminopropionate (**69**) and triethylamine in DMF gave the indole (**70**). Cyclization and removal of the ester group followed lines already described<sup>50</sup> (Scheme 4). Pyrrole **72** gave, on treatment with sodium hydride in DMF, dihydropyrrolizine **73** by an intramolecular alkylation of an ester anion.<sup>51</sup>



SCHEME 4

Enamines are starting materials for the synthesis of benzopyrrolizines. Thus **74** was cyclized in hot acetic anhydride to the hexahydro derivative (**75**), which with palladium chloride in refluxing mesitylene afforded the aromatized

<sup>50</sup> T. Kametani, T. Yamanaka, and M. Satoh, *J. Pharm. Soc. Jpn.* **87**, 1407 (1967).

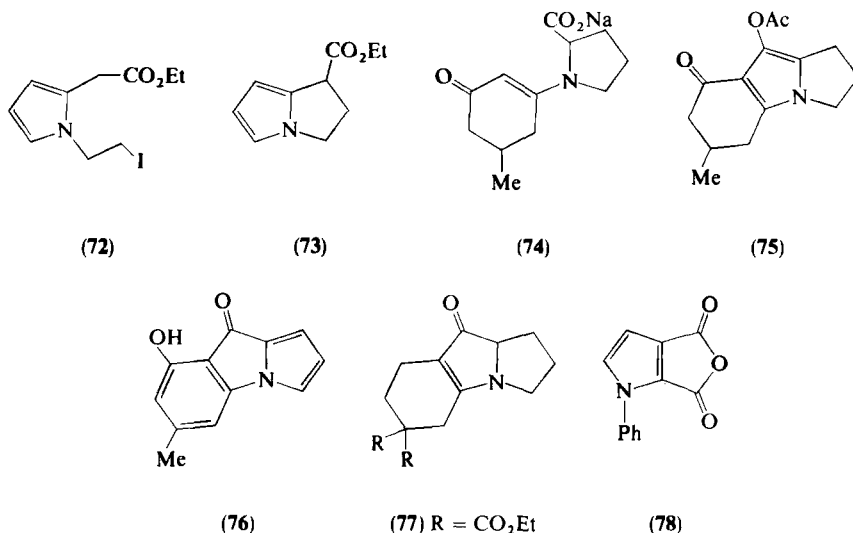
<sup>51</sup> H. Carpio, E. Galeazzi, R. Greenhouse, A. Gúzmán, E. Velarde, Y. Antonio, F. Franco, A. Leon, V. Pérez, R. Sales, D. Valés, J. Ackrell, D. Cho, P. Gallegra, O. Halpern, R. Koehler, M. L. Maddox, J. M. Muchowski, A. Prince, D. Tegg, T. C. Thurber, A. R. van Horn, and D. Wren, *Can. J. Chem.* **60**, 2295 (1982).

benzopyrrolizinone (76).<sup>52</sup> A related method gave perhydro derivatives (77).<sup>53,54</sup>

Friedel–Crafts reactions have found application to form the 1,2-bond of pyrrolizines. Treatment of anhydride 78 with aluminum chloride gave 93% of acid 79, which on heating in the presence of copper gave a 91% yield of 2,3-benzo-1*H*-pyrrolizin-1-one (17).<sup>55</sup> Benzopyrrolizinones (81) have been obtained from acid chlorides (80) by a similar route.<sup>56,57</sup> Houben–Hoesch cyclization of nitrile 82 gave 2,3-benzo-1*H*-pyrrolizin-1-one (17) in a reaction that resembles the formation of 17 from 16a.<sup>58</sup>

Conjugated derivative 84b was obtained in a two-step reaction from bis(phenacyl)aniline via indole 83 by treatment with PPA.<sup>59</sup>

A photo-Fries reaction has been used to synthesize the highly substituted benzopyrrolizinone 85.<sup>60</sup>



<sup>52</sup> R. J. Friary, S. J. M. Gilligan, R. P. Szajewski, K. J. Falci, and R. W. Franck, *J. Org. Chem.* **38**, 3487 (1973).

<sup>53</sup> P. W. Hickmott, K. N. Woodward, and R. Urbani, *J.C.S. Perkin I*, 1885 (1975).

<sup>54</sup> P. W. Hickmott and K. N. Woodward, *J.C.S. Perkin I*, 904 (1976).

<sup>55</sup> E. Laschuvka and R. Huisgen, *Chem. Ber.* **93**, 81 (1960).

<sup>56</sup> R. Giuliano, G. C. Porretta, M. Scalzo, F. Chimenti, and M. Artico, *Farmaco, Ed. Sci.* **27**, 1091 (1972) [*CA* **78**, 84178k (1973)].

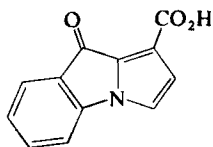
<sup>57</sup> G. Filacchioni, G. C. Porretta, M. Scalzo, and F. Cerreto, *Farmaco, Ed. Sci.* **37**, 353 (1982).

<sup>58</sup> M. Artico, R. Giuliano, G. R. Porretta, and M. Scalzo, *Farmaco, Ed. Sci.* **27**, 60 (1972) [*CA* **76**, 113009x (1972)].

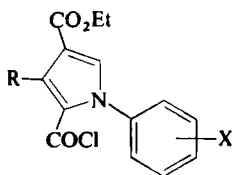
<sup>59</sup> H. Bartsch, *Monatsh. Chem.* **107**, 663 (1976); W. N. Paudler and H. G. Shin, *J. Heterocycl. Chem.* **6**, 514 (1969).

<sup>60</sup> G. J. Siuta, R. W. Franck, and A. A. Ozorio, *J.C.S. Chem. Commun.*, 910 (1974).

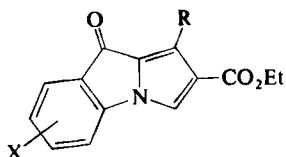




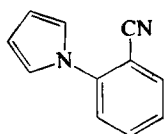
(79)



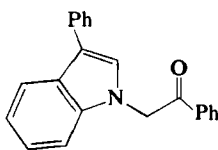
(80)



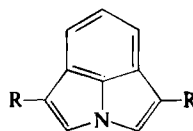
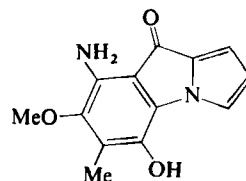
(81)



(82)



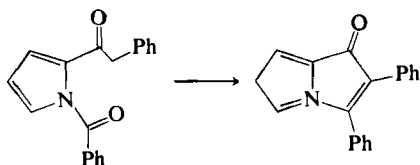
(83)

(84a) R = H  
(84b) R = Ph

(85)

### 3. 2,3-Bond Formation

Scheme 5 shows the only known synthesis in which the 2,3-bond is formed. 2,3-Diphenylpyrrolizin-1-one is prepared by cyclization of a keto amide.<sup>40</sup>

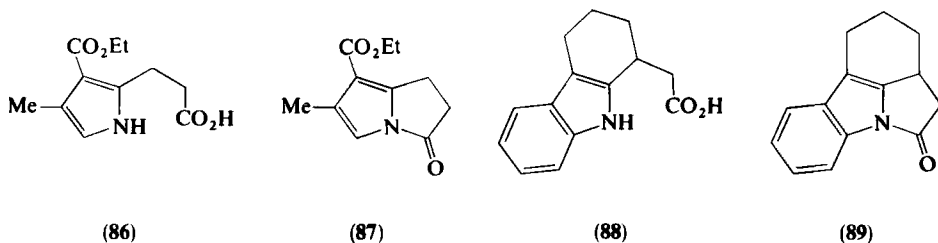


SCHEME 5

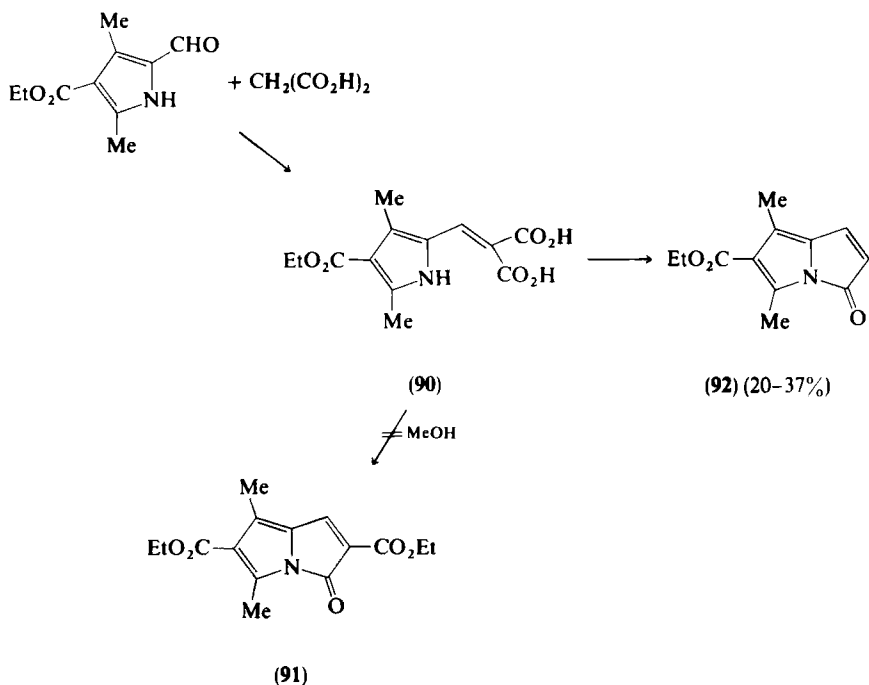
### 4. 3,4-Bond Formation

An early example of an intramolecular acylation of the pyrrole N-atom was provided by H. Fischer who obtained pyrrolizinone **87** from acid **86** using acetic anhydride.<sup>61</sup> The scope of this reaction may be limited because cyclization of the acid **88** to the lactam **89** proceeds in moderate yield.<sup>23</sup>

<sup>61</sup> D. R. Crump, R. W. Franck, R. Gruska, A. A. Ozorio, M. Pagnotta, G. J. Siuta, and J. G. White, *J. Org. Chem.* **42**, 105 (1977); H. Fischer and M. Neber, *Justus Liebigs Ann. Chem.* **496**, 1 (1932).



Several pyrrolizinones have been prepared from pyrrolyl acrylic acid (**90**) and acetic anhydride. The reported synthesis<sup>62</sup> of **91** could not be reproduced; the pyrrolizinone (**92**) was obtained instead (Scheme 6).<sup>63</sup>



SCHEME 6

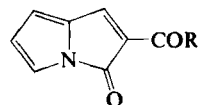
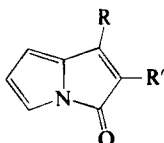
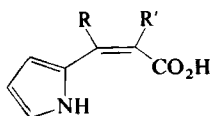
Acids **93a–d** were cyclized to 3*H*-pyrrolizin-3-ones in yields similar to those obtained for **92**. Thus the parent (**94a**) could be obtained either from **93a** or **93b**;<sup>33</sup> the synthesis of **94c** was similar.<sup>64</sup>

<sup>62</sup> W. Küster, E. Brudi, and G. Koppenhöfer, *Ber. Dtsch. Chem. Ges.* **58**, 1014 (1925).

<sup>63</sup> W. C. Agosta, *J. Am. Chem. Soc.* **93**, 2258 (1960).

<sup>64</sup> F. Bohlmann, W. Klöse, and K. Nickisch, *Tetrahedron Lett.*, 3699 (1979).

A reaction of **93b** with phosphorus pentachloride gave **95a**, which was converted to **95b-d** by using conventional methods<sup>65</sup> (see Section III).



(93a) R = R' = H

(93b) R = H, R' = CO<sub>2</sub>H

(93c) R = Me, R' = H

(93d) R = CH<sub>2</sub>COCH<sub>2</sub>Ph, R' = CO<sub>2</sub>H

(94a) R = R' = H

(94b) R = Me, R' = H

(94c) R = CH<sub>2</sub>OCH<sub>2</sub>Ph, R' = H

(95a) R = Cl

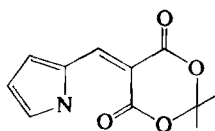
(95b) R = OH

(95c) R = OEt

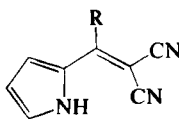
(95d) R = NEt<sub>2</sub>

Pyrrolizin-3-one (**94a**) is formed in 98% yield by flash thermolysis of **96**, which was obtained from 2-formylpyrrole and Meldrum's acid. A possible ketene intermediate then reacts in an intramolecular acylation.<sup>66</sup>

Dinitriles **97** on treatment with bases gave iminopyrrolizines **98a** or aminopyrrolizines **98b**.<sup>67,68</sup> Imine **98a** (R = piperidyl) formed a salt (**99**) with methyl iodide or with Meerwein's salt. Substitution of the dimethylamino group to give derivatives **100** is easily achieved<sup>67</sup> (see Section III).



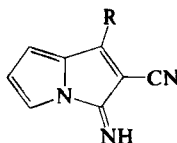
(96)



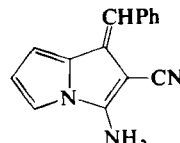
(97a) R = Me

(97b) R = CH<sub>2</sub>Ph

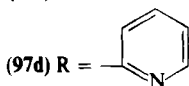
(97c) R = Ph



(98a)

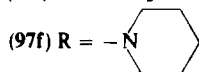


(98b)

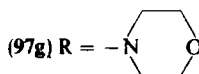


(97d) R = 2-pyridyl

(97e) R = NMe<sub>2</sub>



(97f) R = piperidin-2-yl



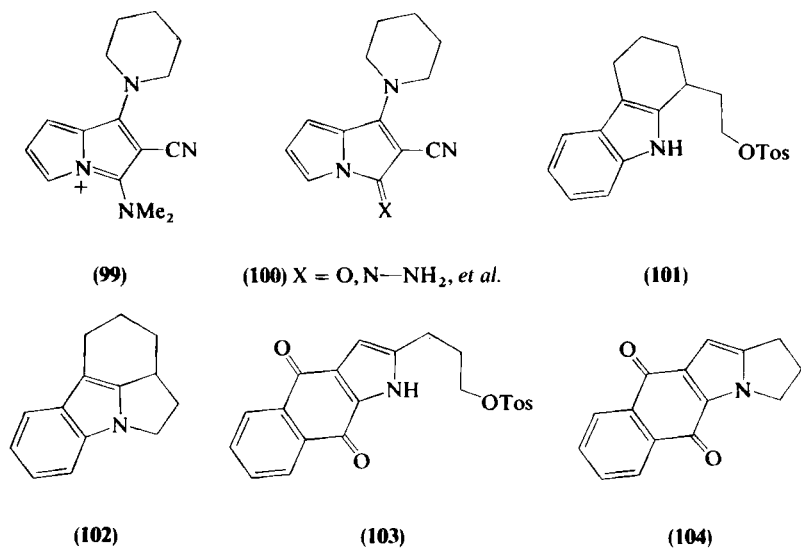
(97g) R = 4-morpholinyl

<sup>65</sup> R. Neidlein and G. Jeromin, *J. Chem. Res., Synop.*, 233 (1980); *J. Chem. Res., Miniprint*, 3090 (1980).

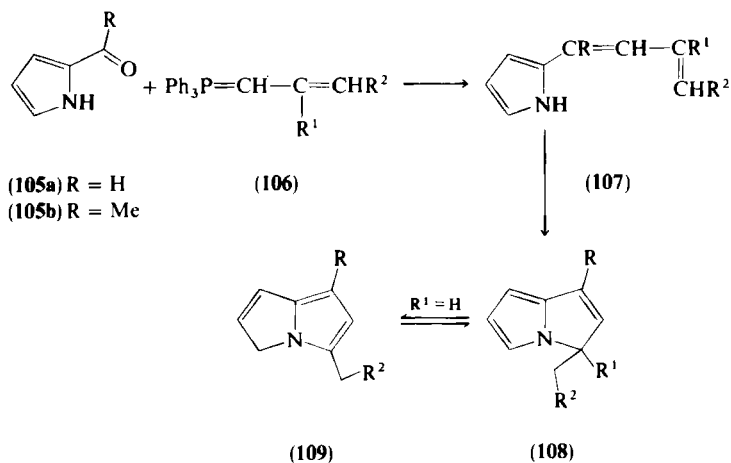
<sup>66</sup> H. McNab, *J. Org. Chem.* **46**, 2809 (1981).

<sup>67</sup> K. Hartke and S. Radau, *Liebigs Ann. Chem.*, 2110 (1974).

<sup>68</sup> R. L. N. Harris, *Aust. J. Chem.* **27**, 2635 (1974).

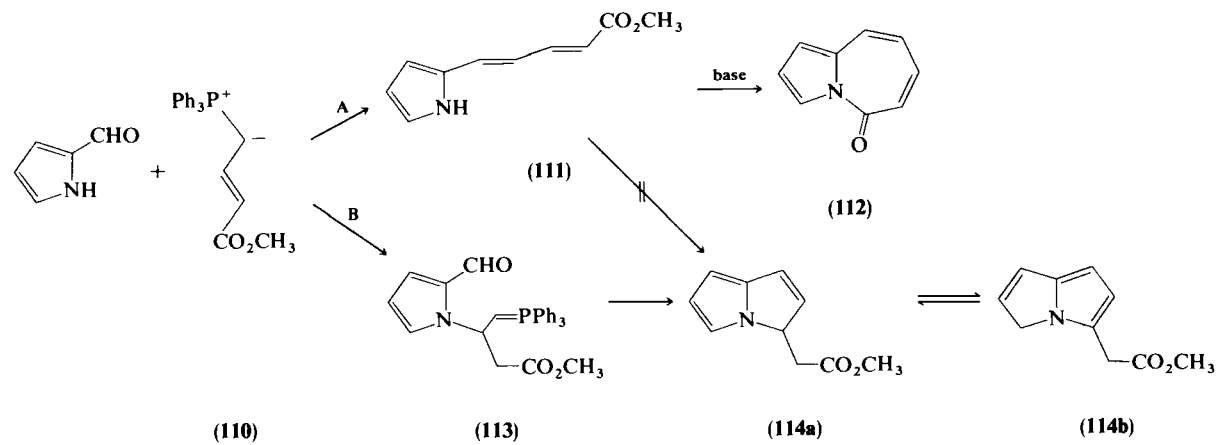


Whereas intramolecular acylation of indole **88** takes place only in moderate yield, the analogous alkylation of indole **101** gives the dihydrodibenzpyrrolizine (**102**) in excellent yield. The reaction conditions for conversion of acid **88** to the tosylate (**101**) are, however, critical.<sup>23</sup> A conversion of tosylate **103** to dihydropyrrolizine **104** was reported.<sup>69</sup>



SCHEME 7

<sup>69</sup> P. Germeraad and H. W. Moore, *J.C.S. Chem. Commun.* 358 (1973); *J. Org. Chem.* **39**, 774 (1974).

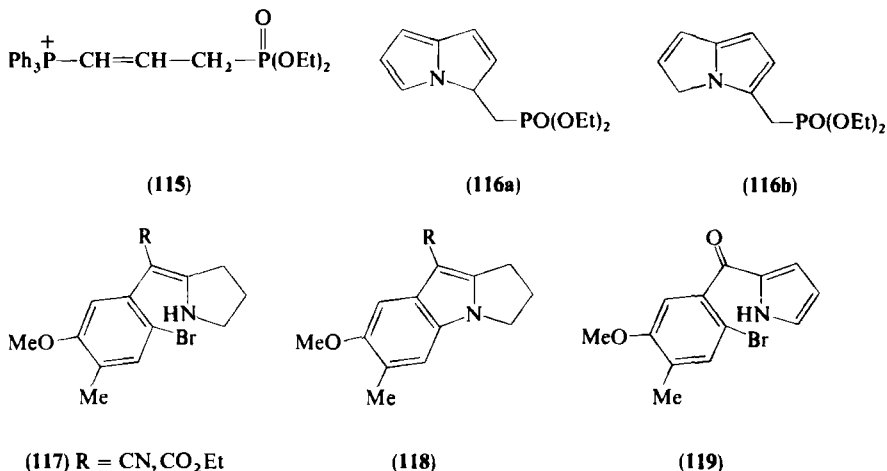


SCHEME 8

Reaction of 2-acylpyrroles with a series of allylphosphoranes gave 3*H*-pyrrolizines. A proposed mechanism is based on the observation that 2-formylpyrrole (**105a**) and phosphorane **106** ( $R^1 = H$ ,  $R^2 = Ph$ ) gave pyrrol-butadiene **107**, which could not be cyclized<sup>70</sup> (see Scheme 7). Rules governing the composition of mixtures (**108** and **109**) are treated in Section III.

A second possible mechanism is outlined, using the reaction of 2-formylpyrrole with the ylide **110** as an example, in Scheme 8. Diene **111**, which is formed in 45% yield during the reaction, cannot be an intermediate in the formation of the pyrrolizines because it does not cyclize to give pyrrolizines **114** on treatment with bases, forming instead the 3*a*-azoniaazulen-4-one (**112**) in good yield. Therefore an addition-elimination sequence (route B) must be taken into consideration.<sup>71</sup> This mechanism is followed in a reaction of phosphonium salt **115** with 2-formylpyrrole, which gave a mixture of isomers **116a** and **116b**.<sup>72</sup>

Pyrrolidines **117** were cyclized by intramolecular aromatic substitution to provide benzopyrrolizine **118**.<sup>73,74</sup> Similarly, benzopyrrolizinone **120** was obtained from pyrrolidine **119**.<sup>75</sup> Reaction of substituted hydroquinone **121** with alkaline potassium ferricyanide afforded a mixture of benzopyrrolizines **122** and **123**.<sup>76</sup> Quinones **124a-c** were converted to benzopyrrolizines **125**



<sup>70</sup> E. E. Schweizer and K. K. Light, *J. Org. Chem.* **31**, 2912 (1966).

<sup>71</sup> W. Flitsch, B. Mütter, and U. Wolf, *Chem. Ber.* **106**, 1993 (1973).

<sup>72</sup> W. Flitsch and F. Jerman, unpublished results.

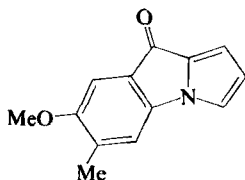
<sup>73</sup> T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *Heterocycles* **3**, 691 (1975).

<sup>74</sup> T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *J.C.S. Perkin I*, 389 (1976).

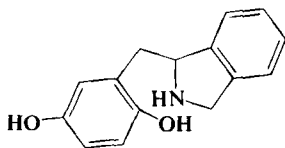
<sup>75</sup> T. Kametani, K. Takahashi, T. Ohsawa, M. Ihara, and K. Fukumoto, *Heterocycles* **4**, 1637 (1976).

<sup>76</sup> T. Takada and S. Ohki, *Chem. Pharm. Bull.* **19**, 977 (1971).

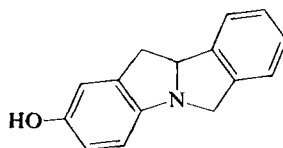
with aluminum amalgam in the presence of water, with sodium borohydride, or with metallic lithium in liquid ammonia, all in poor yield.<sup>77</sup> More simply, a 1:3 mixture of esters **124a** and **124c** was obtained from toluquinone and **126** by a Nenitzescu reaction.<sup>78</sup>



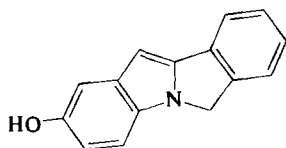
(120)



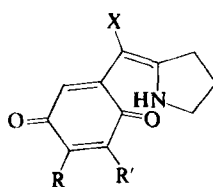
(121)



(122)

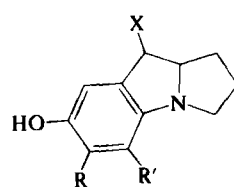


(123)

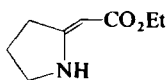


(124a) R = Me, R' = H, X = CN

(124b) R = H, R' = Me, X = CN

(124c) R = H, R' = Me, X = CO<sub>2</sub>Et

(125)



(126)

## B. FORMATION OF TWO BONDS

### 1. 1,8:2,3-Bond Formation

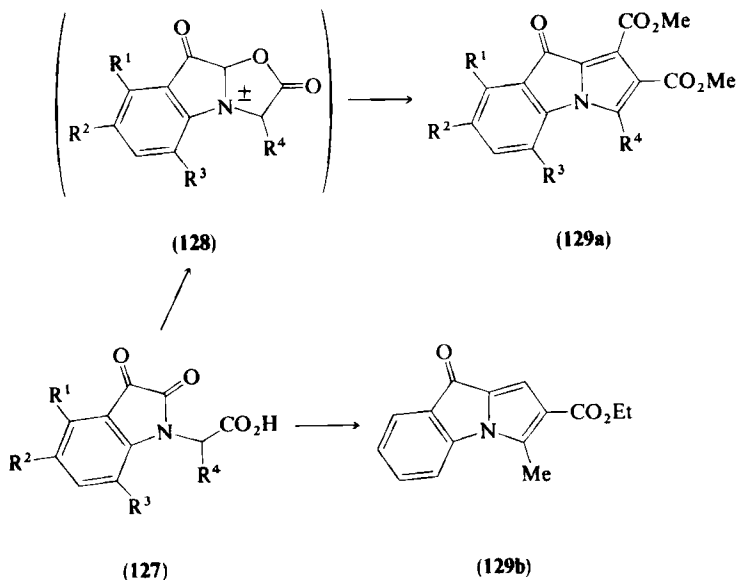
A synthesis of 1-oxo-1*H*-2,3-benzopyrrolizines (**129a**), using a 1,3-dipolar cycloaddition, has been reported.<sup>79</sup> A series of isatins (**121**) on treatment with acetic anhydride formed mesoionic intermediates (**128**), which underwent 1,3-dipolar cycloaddition *in situ* with dimethyl acetylenedicarboxylate to give

<sup>77</sup> Y. Yamada and M. Matsui, *Agric. Biol. Chem.* **34**, 724 (1970).

<sup>78</sup> Y. Yamada and M. Matsui, *Agric. Biol. Chem.* **35**, 282 (1971).

<sup>79</sup> W. K. Anderson and P. F. Corey, *J. Org. Chem.* **42**, 559 (1977).

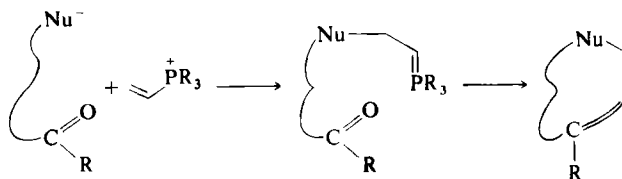
benzopyrrolizinones (**129a**). Ethyl propiolate and **127** gave only **129b** with no evidence of the second possible isomer (see Scheme 9).



SCHEME 9

## 2. 1,2:3,4-Bond Formation

Vinylphosphonium salts accept nucleophiles by addition in a Michael reaction to form phosphoranes, which may subsequently react with a carbonyl group to form an alkene (see Scheme 10). This reaction, discovered by E. E. Schweizer in 1964,<sup>80</sup> was developed into a widely applicable cyclization method.<sup>81</sup> The reaction of 2-formylpyrrole with vinyltriphenylphosphonium bromide to give 87% of 3H-pyrrolizine (**1**) is among the first to



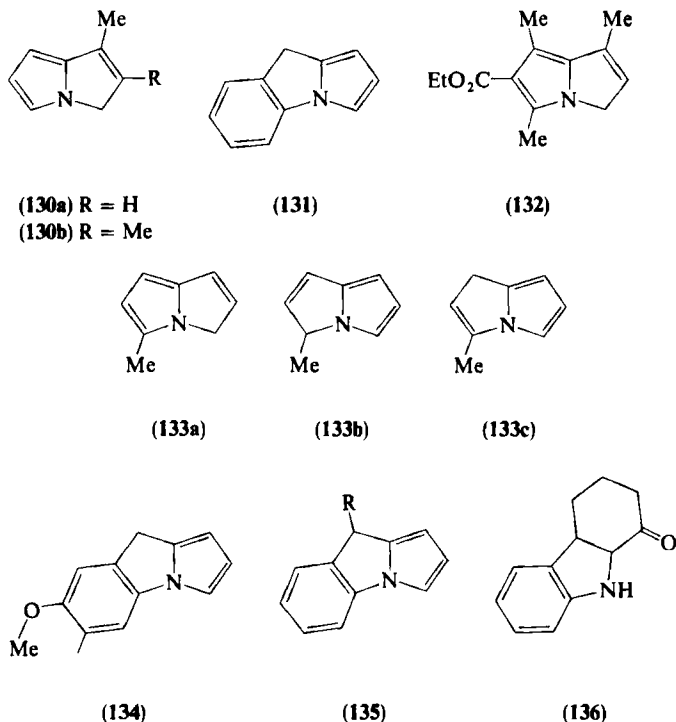
SCHEME 10

<sup>80</sup> E. E. Schweizer, *J. Am. Chem. Soc.* **86**, 2744 (1964).

<sup>81</sup> E. Zbiral, *Synthesis*, 775 (1974); K. B. Becker, *Tetrahedron*, p. 1717 (1980).



have been investigated.<sup>2,82</sup> From 2-acetylpyrrole and 2-acetylindole, 1-methyl-3*H*-pyrrolizine [**130a** (49%)], in a modified procedure,<sup>82</sup> and 1*H*-2,3-benzopyrrolizine [**131** (58%)],<sup>70,82</sup> respectively, were obtained. Compound **130a** is the only isomer observed, as is the pyrrolizine **132**, which was synthesized from the corresponding 2-acetylpyrrole with vinyltriphenylphosphonium bromide.<sup>43</sup> In other cases, however, the cyclization to the pyrrolizine is followed by a tautomeric shift of protons from the 3- to the 5-position and vice versa. Thus 2-formyl-3,4-dimethylpyrrole gave only **130b**, and the expected 6,7-dimethyl-3*H*-pyrrolizine was not observed. A 45:10:45 mixture of isomers **133a-c** was formed from 2-formyl-5-methylpyrrole.<sup>83</sup> The formation of benzopyrrolizines **134**<sup>84</sup> and **135**<sup>23</sup> was reported. The 1-oxotetrahydrocarbazole (**136**) did not give a pyrrolizine by the Schweizer route.<sup>23</sup>



The influence of substituents on both the phosphorus and vinyl groups was investigated (see Scheme 11). Vinylphosphonium salts (**137**) undergo cycliza-

<sup>82</sup> E. E. Schweizer and K. K. Light, *J. Org. Chem.* **31**, 870 (1966).

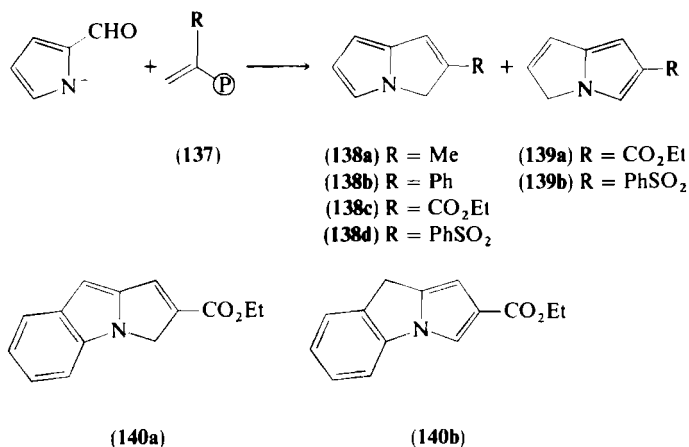
<sup>83</sup> D. Johnson and G. Jones, *J.C.S. Perkin I*, 2517 (1972).

<sup>84</sup> T. Hirata, Y. Yamada, and M. Matsui, *Tetrahedron Lett.*, 19 (1969).

TABLE I  
YIELDS OF PRODUCTS FROM VINYL PHOSPHONIUM SALTS

Structure 137	R	P	Yield (138 + 139) (%)
a	H	$\text{PPh}_3^+$	87 (1)
b	Me	$\text{PPh}_3^+$	67
c	Me	$\text{PPh}_2\text{Me}^+$	25
d	Ph	$\text{PPh}_3^+$	0
e	Ph	$\text{POPh}_2$	82
f	Ph	$\text{PO}(\text{OMe})_2$	45
g	$\text{CO}_2\text{Et}$	$\text{PO}(\text{OMe})_2$	66
h	$\text{PhSO}_2$	$\text{PO}(\text{OMe})_2$	85 (138d) 77 (139b)

tion best when the phosphonium moiety is made more electrophilic, as illustrated in Table I.



SCHEME 11

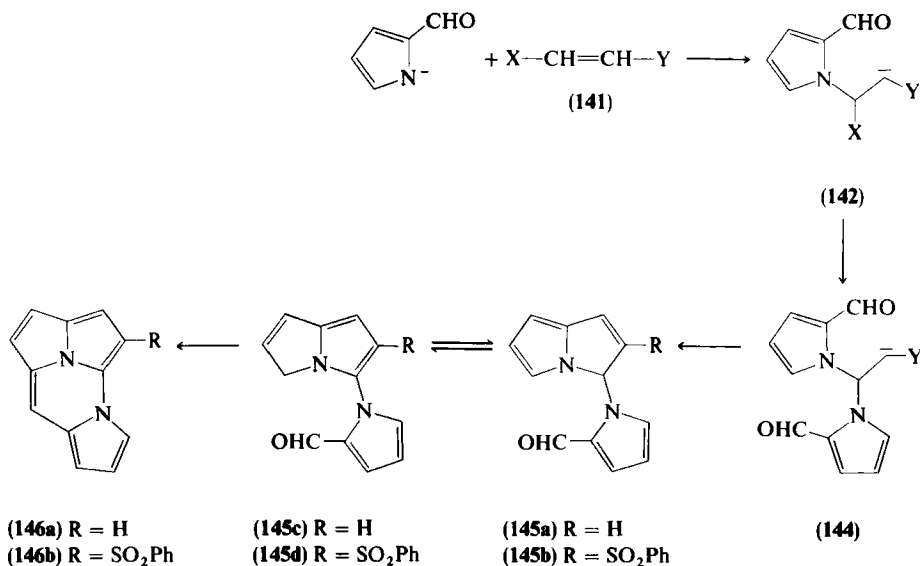
Styrylphosphonium bromide (137d) does not form 2-phenylpyrrolizine (138b) with 2-formylpyrrole and gave low yields with other substrates. Phenylpyrrolizine (138b) was formed in good yield from 2-formylpyrrole and the vinylphosphane oxide (137e) or the vinylphosphonate (137f).<sup>85</sup>

<sup>85</sup> W. Flitsch and V. Batroff, unpublished results.

Pyrrolizine **139a**<sup>86,87</sup> and a mixture of **138d** and **139b**<sup>88</sup> were synthesized in the same way, using phosphonates **137g** and **137h**.

Under controlled reaction conditions, the synthesis of either isomer **138d** (85%) or **139b** (77%) is possible.<sup>88</sup> A reaction of 2-formylindole with phosphonate **137g** gave a mixture of tautomers **140a** (57%) and **140b** (38%).<sup>86</sup>

A reaction of the anion of 2-formylpyrrole with bisphosphonium salt **141** ( $X = Y = \text{PPh}_3^+$ ) yielded pyrrolo[1',2':3,4]pyrimido[2,1,6-*cd*]pyrrolizine (**146a**).<sup>89</sup> A mechanism for this one-pot six-step synthesis, supported by isolation of intermediates **145a** and **145c**, is given in Scheme 12.<sup>90</sup> The yield of **146a** may be enhanced from 30% (with **141**,  $X = Y = \text{PPh}_3^+$ ) to 76% (**141**,  $X = \text{SPh}$ ,  $Y = \text{PPh}_3^+$ ), the latter requiring an average yield of 96% for each step of the sequence. Pyrrolo[2,2,3]cyclazine (**146b**) was obtained from **141** ( $X = Y = \text{SO}_2\text{Ph}$ ) in 50% yield, together with some **147**. A reaction of 2-formylpyrrole with **141** ( $X = \text{SPh}$ ,  $\text{SEt}$ ;  $Y = \text{PPh}_3^+$ ) could be monitored to give 7% of **143a** and 14% of **143b**.



SCHEME 12

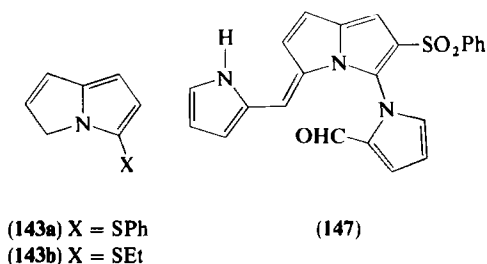
<sup>86</sup> T. Minami, H. Suganuma, and T. A. Agawa, *Chem. Lett.*, 285 (1978).

<sup>87</sup> W. Flitsch, V. Batroff, and W. Lubisch, *Tetrahedron Lett.*, 1947 (1982).

<sup>88</sup> W. Flitsch and W. Lubisch, unpublished results.

<sup>89</sup> W. Flitsch and E. R. Gesing, *Tetrahedron Lett.*, 1997 (1976); *Chem. Ber.* **113**, 614 (1980).

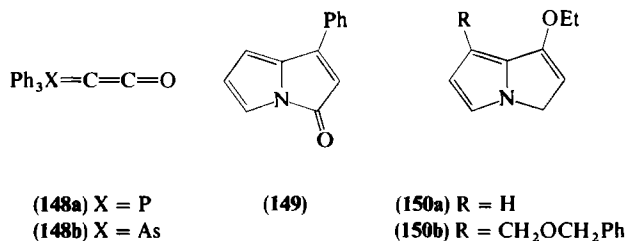
<sup>90</sup> W. Flitsch and W. Lubisch, *Chem. Ber.* **115**, 1547 (1982).



A direct synthesis of 3*H*-pyrrolizin-3-one derivatives has been effected. Reaction of 2-benzoylpyrrole with ylides **148** gave the 3*H*-pyrrolizin-3-one **149**.<sup>91,92</sup> No analogous reaction of 2-formylpyrroles could be achieved with **148a**.<sup>93</sup> Pyrrolizinones **150a**<sup>93</sup> and **150b**,<sup>94</sup> however, were obtained in good yields from the corresponding esters.

From 2-acylpyrroles and keteniminophosphorane (**151**), 3*H*-pyrrolizin-3-imines (**152**) are obtained in 20–50% yield.<sup>91,95</sup>

Cycloaddition reactions have been carried out with corresponding bases of Vilsmeier salts of pyrroles. Thus reaction of **153** with dimethyl acetylenedicarboxylate gave pyrrolizines **154** and 3*a*-azaazulenes **155** in a nonsynchronous reaction. The structure of 3*H*-pyrrolizine **154a** was proved by X-ray analysis.<sup>96</sup> In a closely related reaction, pyrrolizinones **156** and **157** were obtained from the corresponding Vilsmeier salts with phenyl isocyanate.<sup>97</sup> Reaction of 2-*p*-nitrobenzoylindolin-3-one (**158**) with methyl acetoacetate gave the benzopyrrolizinone (**159**).<sup>57</sup>



<sup>91</sup> H. J. Bestmann, G. Schmid, and D. Sandmeier, *Angew. Chem.* **88**, 92 (1976).

<sup>92</sup> H. J. Bestmann and R. K. Bansal, *Tetrahedron Lett.*, 3839 (1981).

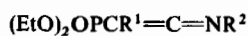
<sup>93</sup> W. Klose, K. Nickisch, and F. Bohlmann, *Chem. Ber.* **113**, 2694 (1980).

<sup>94</sup> K. Nickisch, W. Klose, E. Nordhoff, and F. Bohlmann, *Chem. Ber.* **113**, 3086 (1980).

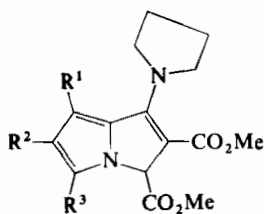
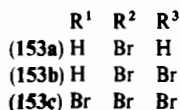
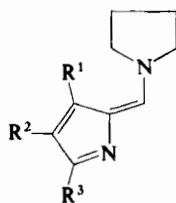
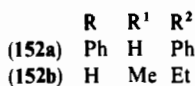
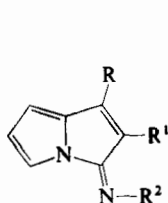
<sup>95</sup> J. Motoyoshiya, J. Enda, Y. Ohshiro, and T. Agawa, *J.C.S. Chem. Commun.*, 900 (1979); J. Motoyoshiya, A. Teranishi, R. Mikoshiba, I. Yamamoto, H. Gotok, J. Enda, L. Okshiro, and T. Agawa, *J. Org. Chem.* **45**, 5385 (1980).

<sup>96</sup> P. E. Sonnet, J. L. Flippen, and R. D. Gilardi, *J. Heterocycl. Chem.* **11**, 811 (1974).

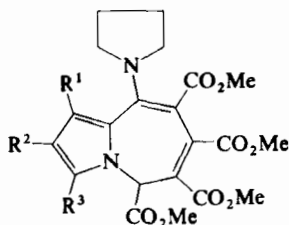
<sup>97</sup> T. Kobayashi, S. Kajigaeshi, and S. Kanemasa, *Heterocycles* **4**, 1281 (1976).



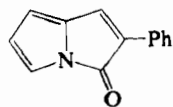
(151)



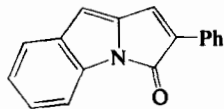
(154)



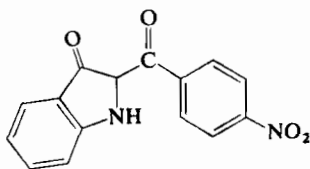
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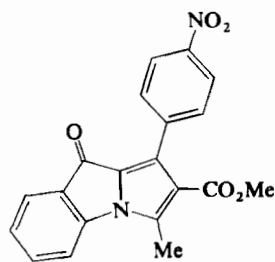
(156)



(157)



(158)



(159)

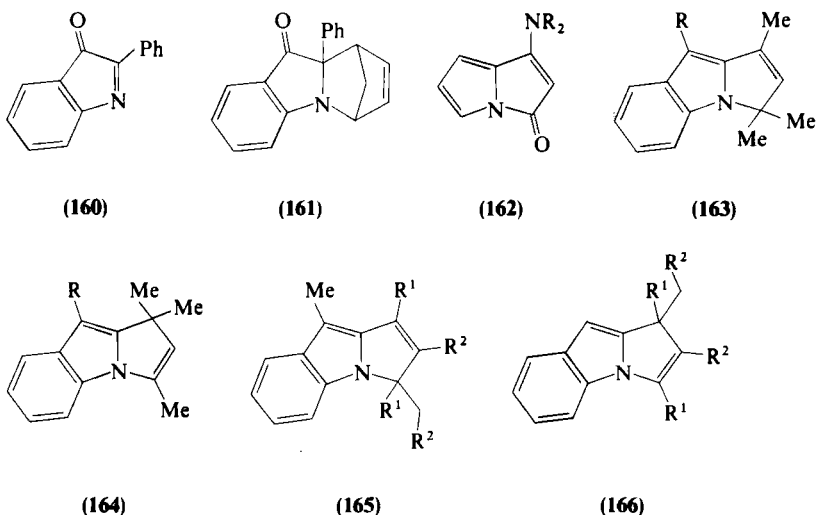
### 3. 1,8:3,4-Bond Formation

The indolone **160** in a Diels–Alder reaction with cyclopentadiene at 20°C in the presence of aluminum chloride or perchloric acid gave **161**.<sup>98</sup>

The central point of another approach involves an electrophilic attack on a pyrrole system. Under the influence of phosphoryl chloride, pyrrole reacts

<sup>98</sup> H. S. Ch'ng and M. Hooper, *Tetrahedron Lett.*, 1527 (1969).

with malonic acid derivatives to give 1-aminopyrrolizin-3-ones (162).<sup>99,100</sup> Condensation of 3-substituted indoles with acetone in the presence of aluminum chloride leads to both possible isomers (163 and 164).<sup>101</sup> Carbon disulfide and 3-methylindole reacted with aluminum chloride to give a complex; subsequent condensation with enolizable ketones such as benzyl methyl ketone and ethyl methyl ketone leads to benzoindolizines 165 and 166.<sup>102</sup>



A synthesis of some benzopyrrolizin-3-ones was found in the course of investigations of reactions of ketenethioacetals.<sup>103</sup> Reaction of 1-acetyl-3-indolinone (167) with methyl 1-cyano-2,2-bismethylthioacrylate (168) in the presence of one equivalent of sodium hydride afforded 169; benzopyrrolizinone 170 was formed when an excess of sodium hydride was used. Treatment of 169 with hydrochloric acid gave pyrrolizinone 171a and its derivative (171b). Reaction of benzopyrrolizinone 170 with amines such as benzylamine gave aminopyrrolizines 172 or 173. Partially hydrogenated pyrrolizinones are easily obtained in high yield from a reaction of imides with cyclopropylphosphonium salt 174 in the presence of sodium hydride. From succinimide, pyrrolizine ester 175 was obtained in a reaction that proceeded via succinimide

<sup>99</sup> A. Ermili, A. J. Castro, and P. A. Westfall, *J. Org. Chem.* **30**, 339 (1965).

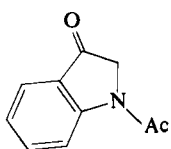
<sup>100</sup> W. C. Anthony, *J. Org. Chem.* **25**, 2049 (1960).

<sup>101</sup> E. Röder, *Arch. Pharm. (Weinheim, Ger.)* **305**, 96, 117 (1972).

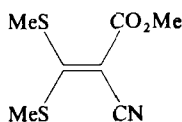
<sup>102</sup> E. Röder and P. Hoechst, *Arch. Pharm. (Weinheim, Ger.)* **308**, 775 (1975).

<sup>103</sup> Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **21**, 1658 (1973); G. Kobayashi, Y. Matsuda, A. Itamura, R. Natsuki, Y. Tominaga, and T. Okamura, *J. Pharm. Soc. Jpn.* **93**, 964 (1973).

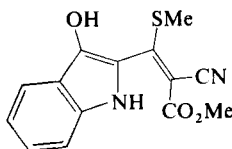
**176.** Similarly, phthalimide gave dihydrobenzopyrrolizinone (**177**).<sup>104,105</sup> Dehydrogenations of pyrrolizine ester **175** are described in Section II.C.



(167)



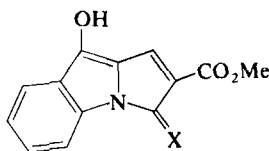
(168)



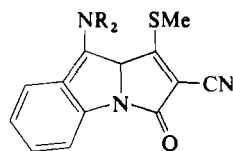
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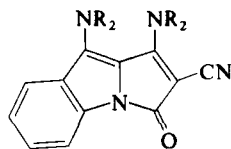
(170)



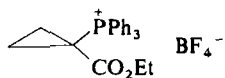
(171a) X = O  
(171b) X = NH



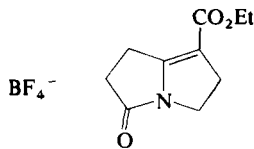
(172)



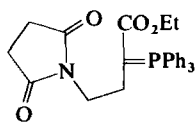
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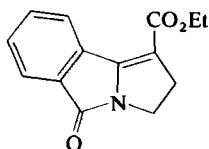
(174)



(175)



(176)



(177)

### C. MISCELLANEOUS METHODS

**1H-2,3-Benzopyrrolizin-1-one (17a)** was first obtained as a minor product in a lithiation and subsequent carboxylation of 1-phenylpyrrole.<sup>106</sup> Cyclization presumably proceeds via the intermediate 1-phenylpyrrole-2-car-

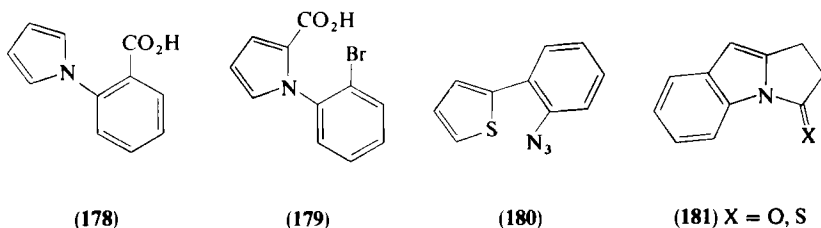
<sup>104</sup> J. M. Muchowski and P. H. Nelson, *Tetrahedron Lett.*, 4585 (1980).

<sup>105</sup> W. Flitsch and P. Wernsmann, *Tetrahedron Lett.*, 719 (1981).

<sup>106</sup> D. A. Shirley, B. H. Grose, and P. A. Poussel, *J. Org. Chem.* **20**, 225 (1955).

boxylic acid. A synthesis of **17a** by intramolecular cyclization of dilithio derivatives, generated either from carboxyphenylpyrrole **178** or from 1-(2'-bromophenyl)pyrrole-2-carboxylic acid (**179**), has been developed.<sup>107</sup>

An intramolecular insertion of an intermediate nitrene occurs when azide **180** is heated in trichlorobenzene at 180°C to give the benzopyrrolizine $\theta$ thione (**181**) in poor yield.<sup>108</sup>



Functionalization of pyrrolizines and partially hydrogenated pyrrolizines has made possible the synthesis of interesting pyrrolizines (see Section III). Only a few examples are presented in this section because most are described in Section III.

The first synthesis of the parent compound (**1**) was reported in 1963,<sup>14</sup> the best route starting from 2,3-dihydropyrrolizin-1-one (**3a**), which was transformed to the corresponding tosylhydrazone (**182**). Compound **1** was obtained from **182** in 29% yield, using Huang–Minlon conditions.

Dehydrogenation of partially hydrogenated pyrrolizines has occasionally been studied. From pyrrolizidines **183**, dihydropyrrolizines **184**, **185**, and **186** were obtained in good yields from reaction with chloranil, manganese dioxide, *N*-oxides and acetic anhydride, using palladium or Raney nickel catalysts.<sup>109</sup> Selective dehydrogenations of **175** have been achieved. Treatment with NBS gave **186**, but with lead tetraacetate, ethyl 1,2-dihydro-3*H*-pyrrolizin-3-one-1-carboxylate (**187**) was formed.<sup>110</sup> The dihydro derivative (**186**) was dehydrogenated with MnO<sub>2</sub> to give pyrrolizinone **188**.<sup>111</sup> Pyrrolizinone **189** was obtained from benzopyrrolizine **131** with singlet oxygen.<sup>112</sup>

<sup>107</sup> M. E. K. Cartoon and G. W. Cheeseman, *J. Organomet. Chem.* **212**, 1 (1981).

<sup>108</sup> G. R. Cliff, G. Jones, and J. McK. Woolard, *Tetrahedron Lett.*, 2401 (1973); *J.C.S. Perkin I*, 2072 (1974).

<sup>109</sup> C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Aust. J. Chem.* **23**, 1869 (1970).

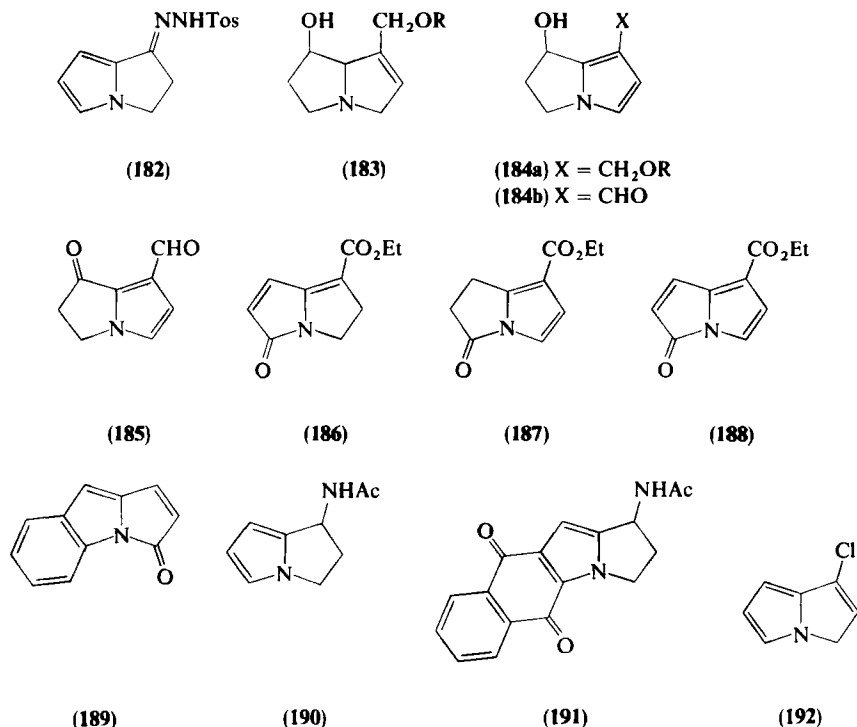
<sup>110</sup> W. Flitsch and P. Russkamp, unpublished results.

<sup>111</sup> W. Flitsch and K. Hampel, unpublished results.

<sup>112</sup> J. Auerbach and R. W. Franck, *J.C.S. Chem. Commun.*, 991 (1969); R. W. Franck and J. Auerbach, *J. Org. Chem.* **36**, 31 (1971); J. Siuta, R. W. Franck, and R. J. Kempton, *ibid.* **39**, 3739 (1974).



Annulation of pyrrolizines may be carried out using the Friedel-Crafts reaction. Quinone derivative **191** was synthesized from pyrrolizine **190** with phthalic anhydride.<sup>113</sup> Formation of 1-chloro-3*H*-pyrrolizine (**192**) was observed in an investigation of the Vilsmeier reaction of 2,3-dihydro-1*H*-pyrrolizin-1-one (**3a**).<sup>17</sup>



### III. Properties

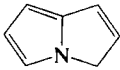
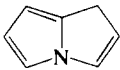
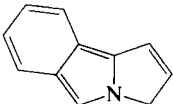
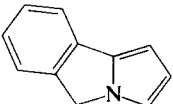
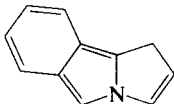
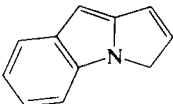
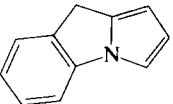
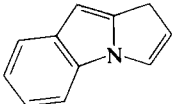
#### A. PHYSICAL PROPERTIES AND THEORETICAL CHEMISTRY

##### 1. Theoretical Chemistry

Depending on the assumptions of simple MO theory, 1*H*-pyrrolizine and 3*H*-pyrrolizine (**1**) either have the same total  $\pi$  energy, being theoretically equivalent to the vinylcyclopentadienyl system, or the 3*H*-pyrrolizine

<sup>113</sup> V. Carelli, M. Cardellini, and F. Morlacchi, *Tetrahedron Lett.*, 765 (1967).

TABLE II  
 RESONANCE STABILIZATION ENERGIES OF ISOMERIC PYRROLIZINES IN  $\beta$  UNITS<sup>114</sup>

		
0.0107	0.0153	
		
0.0160	0.0408	0.0098
		
0.0297	0.0385	0.0278

becomes more stable than the *1H* isomer.<sup>114</sup> Using parameters proposed by Hess and Schaad,<sup>114</sup> resonance energies (REPE values) can be obtained that clearly point to a more stable *3H* isomer (**1**). This is in agreement with experimental results (see Section II,B,1). REPE values of isomeric benzo-pyrrolizines are given in Table II. The report that *1H*-2,3-benzopyrrolizine (**135**, *R* = *H*) is the most stable isomer<sup>115</sup> corresponds with the calculations.

Influences of substituents on the positions of isomeric equilibria that have been calculated<sup>116</sup> by the HMO route do not agree with experimental findings (see Section III,B,1). A correlation of the acidity of *3H*-pyrrolizine (**1**) with the difference in HMO delocalization energies between the pyrrolizine anion and the neutral molecule has been attempted but showed limited success.<sup>115</sup>

The electronic structure of the pyrrolizine anion has been investigated by the HMO-,<sup>115</sup> the ASMO-SCF-MI-,<sup>117</sup> and a CNDO/2-SCF semiempirical method of Pople-Santry-Segal, taking into account all valence electrons

<sup>114</sup> B. A. Hess and L. J. Schaad, *J. Chem Educ.* **51**, 640 (1974).

<sup>115</sup> W. H. Okamura and T. J. Katz, *Tetrahedron* **23**, 2941 (1967).

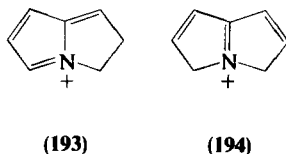
<sup>116</sup> W. Flitsch, unpublished results.

<sup>117</sup> V. Galasso and G. De Alti, *Theor. Chim. Acta* **11**, 411 (1968).

simultaneously.<sup>118</sup> Comparison of the CNDO/2 results with those based on the  $\pi$ -electron approximation shows that the  $\sigma$ -core polarization plays a fundamental role in determining the overall charge distribution and is relatively less important for interpreting the electron spectra.<sup>118</sup> A comparison of HMO  $\pi$  densities with those from proton chemical shifts after correction for the effect of the adjacent ring has nevertheless been successful.<sup>115</sup>

From HMO<sup>115</sup> as well as SCF calculations<sup>117</sup> an electrophilic attack should occur at the 3-position of the pyrrolizine anion, a conclusion that fits experimental findings (see Section III,B,4).

Protonation of 3*H*-pyrrolizine (**1**) takes place at positions 2 and 5, yielding the immonium salts **193** and **194**, respectively, in approximately equal amounts (see Section III,B,4). From HMO calculations, however, **193** is more stable than the cross-conjugated isomer **194**.<sup>116</sup>



Finally, a calculation of the resonance energies of pyrrolizinones, using the method of Hess and Schaad, yields  $\text{REPE} = 0.0155\beta$  for **94a** and  $0.0110\beta$  for **23**, thus explaining the remarkable stability of these compounds.<sup>116</sup>

## 2. Ultraviolet and Visible Spectra

The first collection of data for electronic absorption spectra of 3*H*-pyrrolizines has been assembled in Table III. The parent compound (**1**)<sup>14,82</sup> and simple alkyl derivatives<sup>82,119,120</sup> show two major absorption bands, at 210–220 and 285–295 nm, of approximately equal intensity. A substituent that can extend the conjugation, notably a maleate or fumarate residue as in compounds **195**, produces a considerable shift in the long wavelength band (to 375–391 nm), and the compounds are yellow to orange.<sup>83,120,121</sup> Other conjugating substituents have their maximum effect when placed at positions 1 or 2. Thus the enol acetate (**196**)<sup>14</sup> has a long wavelength band at 320 nm, whereas the 2-acetyl- (**197**)<sup>122</sup> and the 2-alkoxycarbonylpyrrolizines (**198**)<sup>44</sup> show a further bathochromic shift of this band to 350–370 nm. Similar

<sup>118</sup> V. Galasso and G. De Altì, *Gazz. Chim. Ital.* **99**, 1078 (1969) [*CA* **72**, 103994 (1970)].

<sup>119</sup> D. Johnson and G. Jones, *J.C.S. Perkin I*, 840 (1972).

<sup>120</sup> E. E. Schweizer, A. T. Wehman, and D. M. Nycz, *J. Org. Chem.* **38**, 1583 (1973).

<sup>121</sup> D. Johnson and G. Jones, *J.C.S. Perkin I*, 844 (1972).

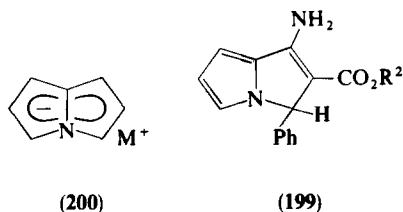
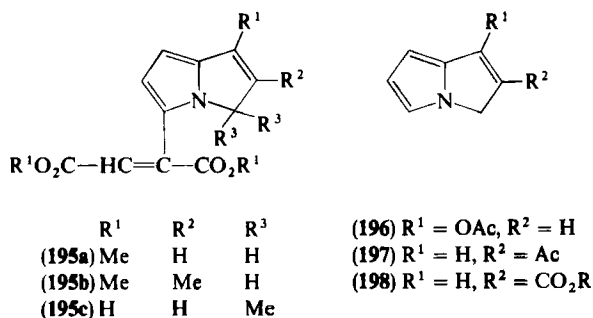
<sup>122</sup> G. Jones and P. M. Radley, *J.C.S. Perkin I*, 1123 (1982).

TABLE III  
UV/VISIBLE SPECTRA OF 3H-PYRROLIZINES

Substituent	Solvent	$\lambda_{\max}$ (log $\epsilon$ )			References
H	EtOH	218 (3.4)		290 (3.78)	14, 82
H (Anion)	THF	210 (4.3)		295 (3.98)	115
1-Me	EtOH			287 (3.79)	82
2-Me		219 (3.56)		295 (3.88)	119
1,2-Me <sub>2</sub>	EtOH	210 (3.77)		285.5 (3.88)	120
1-Me-5[C(CO <sub>2</sub> Me)=CHCO <sub>2</sub> Me]	EtOH	215 sh	240 (4.19) 247 sh	377 (4.32)	120
3,3-Me <sub>2</sub> -5(C(CO <sub>2</sub> Me)=CHCO <sub>2</sub> Me)	EtOH	209 (4.19)		287.5 (3.88) 391 (3.25)	83
1,2-Me <sub>2</sub> -3,5-(C(CO <sub>2</sub> Me)=CHCO <sub>2</sub> Me) <sub>2</sub>	EtOH	209.5 (4.24)	240.5 (4.27) 247 sh	382 (4.21)	121
1-AcO	EtOH	220 (4.08)	240 (3.7)	320 (4.06)	14
2-Ac	EtOH		242 (3.31)	373 (4.07)	122
6-Ac	EtOH		250 (3.31)	292 (2.45)	122
5-CCl <sub>3</sub> CO				358 (3.57)	123
2-MeO <sub>2</sub> C				354 (4.4)	44
2-EtO <sub>2</sub> C				352 (4.4)	44
6-MeO <sub>2</sub> C		223 (4.07)	273 (4.4)		44
6-EtO <sub>2</sub> C		232 (4.6)	273 (4.3)	355 (1.7) <sup>a</sup>	43, 44
7-EtO <sub>2</sub> C		233 (4.08)	258 (3.4) 268 (3.4)	305 (3.94)	124
1-NH <sub>2</sub> -2-CO <sub>2</sub> Me-3-Ph	CH <sub>2</sub> Cl <sub>2</sub>	252 (4.04)	262 sh (3.92)	332 (4.22)	19
1-NH <sub>2</sub> -2-CO <sub>2</sub> Et-3-Ph	CH <sub>2</sub> Cl <sub>2</sub>	252 (4.04)	262 sh (3.95)	331 (4.21)	19, 20
1-NH <sub>2</sub> -2-CO <sub>2</sub> - <i>t</i> -Bu-3-Ph	CH <sub>2</sub> Cl <sub>2</sub>	250 (4.04)	260 sh (3.93)	331 (4.21)	19
6-Br-2,3-(CO <sub>2</sub> Me) <sub>2</sub> -1-( <i>N</i> -pyrrolidinyI)	EtOH	235 (4.09)	281 (4.32)	348 (4.17)	67

<sup>a</sup> Only reported in ref. 44; possibly due to small amounts of 2-EtO<sub>2</sub>C isomer.

conjugating substituents on the pyrrole ring have very little effect on the wavelength of the absorption maxima.<sup>43,44,122-124</sup> A series of 1-amino-2-alkoxycarbonylpyrrolizines of general formula **199** absorb at 250–254 and at 331–332 nm.<sup>19,20</sup> There is surprisingly little difference in electronic absorption between 3*H*-pyrrolizine (**1**) and its anion (**200**)<sup>115</sup>; the latter is a 10  $\pi$ -electron delocalized system. Protonation of 3*H*-pyrrolizines is dealt with in Section III,B,4.



The 3*H*-pyrrolizin-3-ones and related compounds (Table IV) are highly colored. Characteristically, there are bands at 220–240, 290–300, and 410–440 nm. Conjugating substituents have an unpredictable effect. For example, the band at longest wavelength in the 2-phenyl derivative **52a** is at 440 nm,<sup>39</sup> whereas that of the 2,3-diphenyl derivative **52b** is at 490 nm.<sup>40</sup> The spectra of 1*H*-pyrrolizin-1-ones (Table V) are remarkably similar to those of the 3*H*-pyrrolizin-3-ones, although in some cases with more maxima. The 2-chloro- (**21a**), 2-bromo- (**201**), and 2,5-dichloropyrrolizinones (**21b**) have been examined in a number of solvents, including strong acid and Lewis acid media.<sup>26</sup> The Lewis acids cause spectacular bathochromic shifts of the long wavelength band, in one case to 544 nm. Because protonation and Lewis acid complexation are presumably associated with the oxygen atom, this striking effect must be related to a change in polarization along the  $y$ -axis.

<sup>123</sup> S. Brandänge and C. Lundin, *Acta Chem. Scand.* **25**, 2447 (1971).

<sup>124</sup> G. Jones and P. M. Radley, *J. Chem. Res., Synop.*, 54 (1982); *J. Chem. Res., Miniprint* 385 (1982).

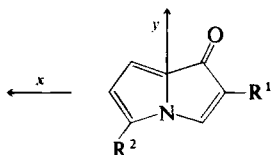
TABLE IV  
UV/VISIBLE SPECTRA OF SUBSTITUTED 3*H*-PYRROLIZIN-3-ONES AND RELATED DERIVATIVES

Substituent	3-X	Solvent	$\lambda_{\max}$ (log $\epsilon$ )				References
H	O	EtOH		292 (5.0)		416 (3.7)	39
1-Me	O	EtOH		285 (3.9)		412 (2.8)	39
2-Ph	O	EtOH		256 (4.1)	293 (3.7)	440 (3.4)	39
1,2-Ph <sub>2</sub>	O		204 (4.58)	252 (4.31)		490 (3.5)	40
2-CO <sub>2</sub> H	O	EtOH	230 (3.98)	302 (3.61)	352 (3.52)	442 (3.06)	65
2-COCl	O	CH <sub>2</sub> Cl <sub>2</sub>	232 (3.79)	264 (3.6)	300 (3.59)	376 (3.56) 465 (3.08)	65
2-CO <sub>2</sub> Et	O	EtOH	230 (4.13)		296 (3.71)	448 (3.16)	65
2-CONEt <sub>2</sub>	O	EtOH	228 (3.83)		294 (3.94)	434 (3.26)	65
1-Me <sub>2</sub> N	O	EtOH	212 (4.13)	274 (4.18)	308 (4.1)	431 (3.32)	100
5,7-Me <sub>2</sub> -6-EtO <sub>2</sub> C	O	Cyclohexane		~ 250 (4.2)	~ 300 (3.78)	439 (3.22)	63
H	NOH	EtOH		293 (4.1)	303 (4.1)	372 (3.3)	43
2-CN-1-( <i>N</i> -piperidinyI)	NH	MeOH	239 (4.36)	287 (4.25)	317.5 (4.29)	445 (3.27)	67
2-CN-1-(2-pyrryl)	NH	MeOH	245 (3.95)	271 (3.72)	323.5 (3.97)	436.5 (4.44) 436 (3.74)	67
2-CO-1-MeS	NH	MeOH	235 (4.0)		348 (3.92)	427 (4.0) 550 sh (2.67)	67
H	CPh <sub>2</sub>	EtOH	242 (4.11)		342 (4.23)	407 sh	115
		Cyclohexane	247 (4.17)		346 (4.23)	413 sh	115
H	C(COPh)Ph	Cyclohexane	228 sh (4.12)	248 (4.2)	333 (4.25)		115
H	C(CO <sub>2</sub> R)-CH <sub>2</sub> (CO <sub>2</sub> R)	EtOH	209.5 (4.14)	230 sh	322.5 (4.3)	420 (3.29)	120
7-Me	C(CO <sub>2</sub> R)-CH <sub>2</sub> (CO <sub>2</sub> R)	EtOH	211.5 (4.18)	235 sh	340 (4.31)	423 (3.44)	120
1,2-Me <sub>2</sub>	C(CO <sub>2</sub> R)-CH <sub>2</sub> (CO <sub>2</sub> R)	EtOH	210 (4.1)		320 (4.09)	400 sh	120

TABLE V  
UV/VISIBLE SPECTRA OF SUBSTITUTED 1*H*-PYRROLIZIN-1-ONES

Substituent	Solvent	$\lambda_{\max}$ (log $\epsilon$ )				References		
H	CH <sub>2</sub> Cl <sub>2</sub>	310 (3.9)		395 (2.4)		26		
2,3-Ph <sub>2</sub>		206 (4.5)	250 (4.24)	332 (4.08)	410 (2.95)	40		
2-CO <sub>2</sub> H	CH <sub>2</sub> Cl <sub>2</sub>	240 (4.32)		330 (4.05)	422 (2.83)	26		
	TFA <sup>a</sup>			330 (4.0)	453 (2.7)	26		
2-COCl	CH <sub>2</sub> Cl <sub>2</sub>	258 (4.4)		330 (4.0)	420 (3.1)	26		
	TFA		312 (4.02)	330 sh (3.9)	454 (2.7)	26		
2-CO <sub>2</sub> Et	CH <sub>2</sub> Cl <sub>2</sub>		294 (3.87)	323 (3.95)	418 (2.79)	26		
	TFA		310 (3.94)	326 sh (3.92)	454 (2.58)	26		
2-Cl	MeOH	246 (3.3)	300 (3.97)		404 (2.5)	26		
	CH <sub>2</sub> Cl <sub>2</sub>	240 (3.3)	315 (4.1)		418 (2.5)	26		
	TFA		322 (4.09)		430 (2.3)	26		
	CH <sub>2</sub> Cl <sub>2</sub> + SbCl <sub>5</sub>				544 (2.3)	26		
2-Br	CH <sub>2</sub> Cl <sub>2</sub>	234 (3.3)	317 (4.1)		420 (2.6)	26		
2,5-Cl <sub>2</sub>	Hexane		300 (3.93)	323 (3.95)	335 (3.75)	392 (2.61)	26	
	MeOH			310 (4.02)		400 (2.96)	26	
	CH <sub>2</sub> Cl <sub>2</sub> + H <sub>2</sub> SO <sub>4</sub>		310 (3.9)	324 (3.94)	337 (3.75)	420 (2.55)	26	
	H <sub>2</sub> SO <sub>4</sub>			340 (3.96)	354 (3.91)	372 (3.68)	500 (2.3)	26
	CH <sub>2</sub> Cl <sub>2</sub> + SbCl <sub>5</sub>			354 (4.07)	376 (3.83)	500 (2.38)		26
	TFA		332 (4.07)	426 sh (3.46)		442 (3.01)		26

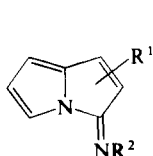
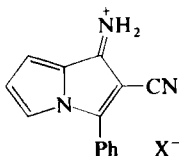
<sup>a</sup> TFA, Trifluoroacetic acid.

(201)  $R^1 = \text{Br}$ ,  $R^2 = \text{H}$ 

### 3. Infrared Spectra

Apart from the normal absorption bands of substituents, most interest in the IR spectra of pyrrolizine derivatives is associated with the double bond stretching region in pyrrolizinones. The carbonyl band in 3*H*-pyrrolizin-3-ones is at  $1730\text{--}1745\text{ cm}^{-1}$  (parent at  $1740\text{ cm}^{-1}$ ). The presence of an amino group at position 1 shifts the carbonyl absorption to longer wavelength ( $1710\text{--}1725\text{ cm}^{-1}$ , vinylogous amide<sup>99</sup>). In contrast, the carbonyl stretch of 1*H*-pyrrolizin-1-ones is at  $1690\text{ cm}^{-1}$ <sup>26</sup>; 2,5-dichloropyrrolizinone (21b) shows a slight shift to shorter wavelength with a carbonyl absorption at  $1710\text{ cm}^{-1}$ .

The 3*H*-pyrrolizin-3-imines (202) show  $\text{C}=\text{N}$  absorption at  $1650\text{--}1660\text{ cm}^{-1}$ <sup>67,95</sup>; the only comparable example of a pyrrolizin-1-imine (203) has an absorption at  $1640\text{ cm}^{-1}$  ( $\text{C}=\text{N}^+$ ).<sup>19</sup> Most compounds of either type also have distinctive double bond absorption in the  $1590\text{--}1610\text{ cm}^{-1}$  region.

(202)  $R^2 = \text{H}$  or Et

(203)

### 4. $^1\text{H}$ -NMR Spectra

The  $^1\text{H}$ -NMR shifts and coupling constants for unsubstituted and substituted 3*H*-pyrrolizines have been grouped in Table VI.<sup>125–127</sup> The spectral data for 3*H*-pyrrolizin-3-ones are in Table VII, and those of 1*H*-pyrrolizin-1-ones and related compounds in Table VIII. There are no examples of pure

<sup>125</sup> R. Heidhues, Ph. D. Thesis, University of Münster, pp. 38–56 (1967).

<sup>126</sup> W. Flitsch, R. Heidhues, and H. Paulsen, *Tetrahedron Lett.*, 1181 (1968).

<sup>127</sup> S. Mori, M. Watanabe, S. Kajigaeshi, and S. Kanemasa, *Heterocycles* **4**, 957 (1976).



TABLE VI  
<sup>1</sup>H-NMR DATA FOR 3*H*-PYRROLIZINES

Substituent	Solvent	H1	H2	H3	H5	H6	H7	Other	<i>J</i> values (Hz)	References
H	Neat	6.2	5.63	3.75	6.54	6.08	5.77		1,2 = 6.2; 2,3 = 2.2; 5,6 = 2.7	82, 125, 126
	Benzene- <i>d</i> <sub>6</sub>	6.2	5.58	3.7	6.57	6.2	5.9		6,7 = 3.5; 1,3 = 2.2; 1,5 = 0.6	
	CS <sub>2</sub>	6.44	5.72	4.27	6.7	< 5.9–6.1 >			2,6 = 1.0; 3,5 = 0.3; 5,7 = 1.1	
	MeOH- <i>d</i> <sub>4</sub>	6.37	5.9	4.05	6.8	6.12	5.9			
H (Anion)	THF	4.75	6.03	6.43	6.43	6.03	4.75		1,2 = 2.1; 2,3 = 3.2; 1,3 = < 1	115
1-Me	Neat	—	5.5	3.9	6.72	6.25	5.93	1.9 (3H)	Me,2 = 2.2; 2,3 = 2.2; 5,6 = 2.5	82, 125, 126
	CS <sub>2</sub>	—	5.5	4.0	6.55	5.95	5.62		6,7 = 3.2; Me,3 = 1.5; 2,6 = 1.0; 3,5 = 0.7; 5,7 = 1.0	
2-Me		6.4	—	4.18	6.0	5.92	5.5	1.95 (3H)	1,3 = 0.8; 1,Me = 1.0; 5,6 = 3; 6,7 = 3	119
3-Me								1.91 (3H)		83
5-Me				4.02						83
2-Ph	CDCl <sub>3</sub>	7.0 <sup>a</sup>	—	4.94	7.08 <sup>a</sup>	6.14	5.9		5,6 = 2.7; 6,7 = 3.5	87
2-CH <sub>3</sub> CO	CDCl <sub>3</sub>	6.1	—	4.6	7.2	6.9	6.2	2.35 (3H)		122
5-CH <sub>3</sub> CO	CDCl <sub>3</sub>	← 6.6 →		4.7	—	6.9	5.85	2.3 (3H)	6,7 = 3	123
5-CHCl <sub>2</sub> CO	CDCl <sub>3</sub>	← 6.6 →		4.7	—	7.1	6.1	6.4 (1H)	6,7 = 3	123
5-CCl <sub>3</sub> CO	CDCl <sub>3</sub>	← 6.6 →		4.7	—	7.3	6.1		6,7 = 3	123
6-CH <sub>3</sub> CO	CDCl <sub>3</sub>	6.2	6.5	4.45	7.5	—	6.28	6.35 (3H)	1,2 = 5	122
2-PhCO	CS <sub>2</sub>	7.02?	—	4.74	7.32?	6.25	6.25			125, 126
6-PhCO	CS <sub>2</sub>	6.55	6.22	4.43	< 7.75–7.3 >		6.27	7.75–7.3 (5H)	1,2 = 6; 2,3 = 2.0; 1,3 = 2.0; 3,5 = 1.6	125, 126
3-MeO <sub>2</sub> CCH <sub>2</sub>		6.4	6.0	4.7	6.72	6.0	5.75			71
5-MeO <sub>2</sub> CCH <sub>2</sub>				3.48 <sup>b</sup>						71
2-MeO <sub>2</sub> C	CDCl <sub>3</sub>	7.05	—	4.69	7.44	6.24	6.36	3.82 (3H)		44
2-EtO <sub>2</sub> C	CDCl <sub>3</sub>	7.05	—	4.64	7.41	6.20	6.33	1.32 (3H), 4.18 (2H)		44
6-MeO <sub>2</sub> C	CS <sub>2</sub>	6.53	6.18	4.44	7.33	—	6.17	3.68 (3H)	1,2 = 6.0; 2,3 = 2.0; 1,3 = 1.0; 3,5 = 1.0; 5,7 = 1.0	125–127
6-EtO <sub>2</sub> C	CDCl <sub>3</sub>	6.32	6.2	4.48	7.58	—	6.6	1.32 (3H), 4.25 (2H)		44, 127
5-EtS	Acetone- <i>d</i> <sub>6</sub>	6.6	6.25	4.26	—	6.4	5.96	2.66 (2H), 1.21 (3H)	1,2 = 6.2; 1,3 = 2.0; 6,7 = 3.6; CH <sub>2</sub> , 7 = 1.0	90
5-PhS	Acetone- <i>d</i> <sub>6</sub>	6.72	6.42	4.37	—	6.56	6.4		1,2 = 6.0; 2,3 = 2.1; 1,3 = 2.1; 6,7 = 3.5	90

1,2-Me <sub>2</sub>	CDCl <sub>3</sub>	—	—	4.0	6.6	6.0	5.6	1.82 (3H), 1.82 (3H)	6,7 = 4	83, 120
3,3-Me <sub>2</sub>	Neat					5.88 <sup>a</sup>		1.15 (6H)		70
1,3,3-Me <sub>3</sub>	Neat	—	6.25	—	6.6	5.9	5.58	1.2 (6H), 1.98 (3H)		70
1-Me-5- (CCO <sub>2</sub> Et=CHCO <sub>2</sub> Et)	CCl <sub>4</sub>	—	6.07	3.9	—	6.54	6.07	5.72 (1H), 4.2 (4H), 2.05 (3H), 1.29 (6H)	1,2 = 6; 1,3 = 2; 6,7 = 3.6	120
6-PhSO <sub>2</sub> -5-X <sup>d</sup>	Acetone- <i>d</i> <sub>6</sub>	6.32	6.63	4.15	—	—	6.53			90
6-Ac-7-Me	CDCl <sub>3</sub>	6.1	6.7	4.5	6.9	—	—		1,2 = 5	122
1,3-Me <sub>2</sub> -2-Ac	CS <sub>2</sub>	—	—	4.8	6.9	—	6.3	1.55 (3H), 2.4 (3H), 2.45 (3H)		42
5,7-Me <sub>2</sub> -6-Ac	CS <sub>2</sub>	6.55	6.12	4.26	—	—	—	2.3–2.45 (9H)	1,2 = 6	42
3,3-Me <sub>2</sub> -5- [C(CO <sub>2</sub> Me)= C(CO <sub>2</sub> Me)H]	CDCl <sub>3</sub> ( <i>cis</i> )	6.35	6.14	—	—	5.85	6.35	1.65 (6H), 3.65, 3.8 (2 × 3H), 6.13 (1H)	1,2 = 6; 6,7 = 4	83
	CDCl <sub>3</sub> ( <i>trans</i> )	6.38	6.0	—	—	5.74	6.0	1.31 (6H), 3.50, 3.65 (2 × 3H), 6.87 (1H)	6,7 = 4	83
1,2-Me <sub>2</sub> -3,5- [C(CO <sub>2</sub> Me)= C(CO <sub>2</sub> Me)] <sub>2</sub>	CDCl <sub>3</sub>	—	—	5.27	—	5.99	6.51	3.7–3.92 (4 × 3H), 5.88 (s)	6,7 = 3	121
1-Amino-2- cyano-3-phenyl	CDCl <sub>3</sub>	—	—	5.67	6.8	← 6.33 →				19
1-Amino-2- (MeO <sub>2</sub> C)-3- phenyl	CDCl <sub>3</sub>	—	—	5.55	6.6	← 6.2 →				19
1-Amino-2- (EtO <sub>2</sub> C)-3- phenyl	CDCl <sub>3</sub>	—	—	5.63	6.63	← 6.22 →				19, 20
1-Amino-2- ( <i>t</i> -BuO <sub>2</sub> C)- 3-phenyl	CDCl <sub>3</sub>	—	—	5.68	6.7	← 6.3 →				19, 20
6-Bromo-2,3- dimethoxy- carbonyl-1- pyrrolidiny]	CDCl <sub>3</sub>	—	—	5.42	6.28	—	6.95			127

<sup>a</sup> May be interchanged.<sup>b</sup> Only figure given.<sup>c</sup> No assignment.<sup>d</sup> X = CHO

TABLE VII  
<sup>1</sup>H-NMR DATA FOR SUBSTITUTED 3*H*-PYRROLIZIN-3-ONES AND RELATED DERIVATIVES

Substituent	3-X	Solvent	H1	H2	H5	H6	H7	Other	<i>J</i> values (Hz)	References
H	O	CS <sub>2</sub>	7.1	5.61	6.83	5.97	5.97		1,2 = 6.0	39
1-Me	O	CS <sub>2</sub>	—	5.3	6.77	5.95	5.95			39
2-Ph	O	CS <sub>2</sub>	7.14	—	6.87	6.0	6.0			39
		CDCl <sub>3</sub>	7.05	—	6.83	←5.92→				97
2-CO <sub>2</sub> H	O	DMSO- <i>d</i> <sub>6</sub>	8.1	—	7.29	6.23	6.52	11.89 (1H)		65
2-COCl	O	Acetone- <i>d</i> <sub>6</sub>	8.07	—	7.18	6.24	6.51		5,6 = 3.1; 6,7 = 3.18; 5,7 = 3.1	65
2-CO <sub>2</sub> Et	O	CDCl <sub>3</sub>	7.84	—	7.04	6.14	6.35		5,6 = 3.08; 6,7 = 3.16	65
2-CONEt <sub>2</sub>	O	Acetone- <i>d</i> <sub>6</sub>	7.39	—	7.03	6.12	6.24		5,6 = 3.08; 6,7 = 3.15; 1,5 = 0.6	65
1-Me <sub>2</sub> N	O	CDCl <sub>3</sub>	—	4.22	6.98	←6.06→	3.12 (6H)			99
1-Et <sub>2</sub> N	O	CDCl <sub>3</sub>	—	4.3	7.03	←6.1→	1.29 (6H) 3.45 (4H)			99
1-Et <sub>2</sub> N-5,7-Me <sub>2</sub> -6-Et	O	CDCl <sub>3</sub>	—	4.36	—	—	—	1.18 (9H), 2.1 (3H), 2.28 (3H), 2.32 (2H), 3.42 (4H)		99
1-PhCH <sub>2</sub> O	O	CDCl <sub>3</sub>	—	4.80	6.95	6.05	6.15		5,6 = 2; 6,7 = 2.5	94
7-PhCH <sub>2</sub> OCH <sub>2</sub> -1-EtO	O	CDCl <sub>3</sub>	—	4.73	6.96	6.14	—			93
THPOCH <sub>2</sub> -1-EtO	O	CDCl <sub>3</sub>	—	4.70	6.93	6.10	—			93

2-CN-1-( <i>N</i> -piperidyl)	NH	DMSO- <i>d</i> <sub>6</sub>	—	—	7.55	6.38	6.73	8.55	5,6 = 2.8; 6,7 = 3.5; 5,7 = 0.8	67
2-CN-1-(2-pyrryl)	NH	DMSO- <i>d</i> <sub>6</sub>	—	—	7.63	6.43	7.07	8.67	6,5 = 2.8; 6,7 = 3.5; 5,7 = 0.8	67
2-CN-1-Me <sub>2</sub> N	NH	DMSO- <i>d</i> <sub>6</sub>	—	—	7.59	6.69	9.97	9.97	5,6 = 2.8; 6,7 = 3.6; 5,7 = 0.8	67
					7.35	←6.35→	7.45			68
H	NOH		6.79	6.2	7.55	6.2	6.2	9.64	5,6 = 2.5; 5,7 = 1.0; 1,2 = 5.8	43
2-Me	NEt	CDCl <sub>3</sub>	6.9	—	6.46	6.05	5.76	1.41 (3H), 1.96 (3H), 3.57 (2H)		95
H	CHNMe <sub>2</sub>	TFA	6.65	7.5	4.9 <sup>b</sup>	<6.75–7.05>		8.3 (NCH), 3.75 (3H), 3.60 (3H)		128
7-Cl-1,5-(CHO) <sub>2</sub>	CHNMe <sub>2</sub>	TFA	—	7.61	—	7.0	—	9.3 (CHN)		67
H	CPh <sub>2</sub>	CCl <sub>4</sub>	6.36	6.11	<5.78, 5.61>		7.08 (5H), 7.18 (5H)	1,2 = 5.9		115
H	C(CO <sub>2</sub> R)- CH <sub>2</sub> CO <sub>2</sub> R	CCl <sub>4</sub>	7.17	6.59	6.93	6.1	5.95	<i>a</i>	1,2 = 6.5; 5,6 = 3; 6,7 = 3	120
7-Me	C(CO <sub>2</sub> R) CH <sub>2</sub> CO <sub>2</sub> R	CCl <sub>4</sub>	7.13	6.61	6.82	5.9	—	<i>a</i>	1,2 = 6; 5,6 = 3	120
1,2-Me <sub>2</sub>	C(CO <sub>2</sub> R) CH <sub>2</sub> CO <sub>2</sub> R	CCl <sub>4</sub>	—	—	6.92	6.62	5.76	<i>a</i>	5,6 = 3; 6,7 = 3	120

<sup>a</sup> Ester signals and CH<sub>2</sub>, δ 3.6.

<sup>b</sup> Two proton signal due to protonated form.

TABLE VIII  
<sup>1</sup>H-NMR DATA FOR SUBSTITUTED 1H-PYRROLIZIN-1-ONES AND DERIVATIVES

Substituent	1-X	Solvent	H2	H3	H5	H6	H7	Other	J values (Hz)	References
H	O	CD <sub>2</sub> Cl <sub>2</sub>	5.47	7.55	6.75	6.25	6.62		2,3 = 4.11; 5,6 = 2.64; 6,7 = 3.52; 2,6 = 0.9; 5,7 = 0.9; 3,7 = 0.9	26
2-CO <sub>2</sub> H	O	TFA- <i>d</i> <sub>1</sub>	—	8.53	7.1	6.44	7.1			26
2-COCl	O	CD <sub>2</sub> Cl <sub>2</sub>	—	8.24	6.97	6.33	6.9		6,7 = 3.6; 5,6 = 2.9; 5,7 = 0.9	26
2-CO <sub>2</sub> Et	O	CDCl <sub>3</sub>	—	8.26	6.87	6.27	6.74		6,7 = 3.45; 5,6 = 2.86	26
		Acetone- <i>d</i> <sub>6</sub>	—	8.6	7.16	6.33	6.33		3,7 = 1.0	
2-Cl	O	Acetone- <i>d</i> <sub>6</sub>	—	8.04	7.09	6.22	6.77		5,6 = 2.64; 6,7 = 3.67	26
		CD <sub>2</sub> Cl <sub>2</sub>	—	7.5	6.79	6.18	6.74		3,7 = 0.88	
		TFA- <i>d</i> <sub>1</sub>	—	7.43	6.88	6.23	6.97			
		CD <sub>2</sub> Cl <sub>2</sub> + SnCl <sub>4</sub>	—	7.34	6.93	6.21	7.24			26
2-Br	O	Acetone- <i>d</i> <sub>6</sub>	—	8.14	7.09	6.22	6.78		5,6 = 2.64; 6,7 = 3.67; 5,7 = 0.88; 3,7 = 0.88	26
2,5-Cl <sub>2</sub>	O	CD <sub>2</sub> Cl <sub>2</sub>	—	7.55	—	6.06	6.7		6,7 = 3.81; 3,7 = 0.9	26
		TFA- <i>d</i> <sub>1</sub>	—	7.49	—	6.1	7.49			
		CD <sub>2</sub> Cl <sub>2</sub> -HBF <sub>4</sub>	—	7.42	—	6.17	7.38			
2-CN-3-Ph	N <sup>+</sup> H <sub>2</sub>	Acetone- <i>d</i> <sub>6</sub>	—	—	7.93	6.65	7.93			70
2-CN-3-NH <sub>2</sub>	CHPh							6.74(CHPh)		68

1*H*-pyrrolizines, but Johnson and Jones<sup>83</sup> have attributed a signal at  $\delta$  3.13 to the H1 methylene group of compound 133c. A very detailed study of 3*H*-pyrrolizine (**1**) has been given by Heidhues<sup>125</sup> and the shifts and coupling constants for the neat liquid are given in Fig. 1. Noteworthy are the upfield positions of H2 and H7, the downfield positions of H1 and H5, and the major coupling constants, particularly  $J_{1,2} = 6.2$  Hz and  $J_{2,3} = 2.2$  Hz; long-range couplings are observed between H1 and H3, H1 and H5, and, more surprisingly, between H3 and H7, and between H2 and H6. The chemical shifts are little changed for solution in benzene-*d*<sub>6</sub>, but downfield shifts, particularly in the signals for H2, H3, and H5, are observed for solutions in carbon disulfide or methanol. The <sup>1</sup>H-NMR spectra have been crucial in assigning structures to potentially tautomeric pairs of compounds because a 3H → 5H shift of hydrogen occurs readily (see Section III,B,1).

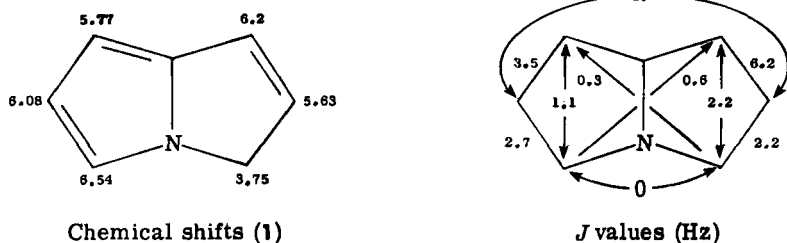


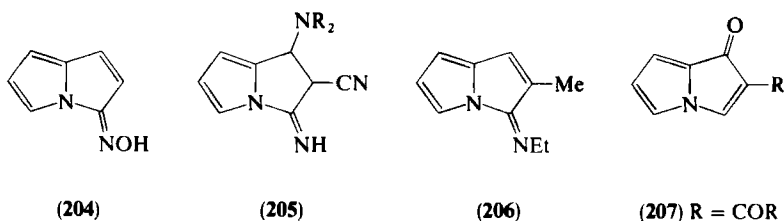
FIG. 1. Chemical shifts and coupling constants for 3*H*-pyrrolizine.

Okamura and Katz reported the spectrum of the anion **200** with various associated cations.<sup>115</sup> They assigned the upfield signal to H1 and the downfield signal to H3 and attempted to correlate charge densities calculated from the NMR data with those from HMO calculations. The same authors present the spectrum of 3-deuterio-3*H*-pyrrolizine; deprotonation of this might provide firmer evidence for the assignments on the anion. Protonation of 3*H*-pyrrolizine gives a mixture of 2*H*,3*H*- and 3*H*,5*H*-pyrrolizinium cations<sup>43</sup> as does 1-methyl-3*H*-pyrrolizine (see Section III,B,4).

The spectral data for 3*H*-pyrrolizin-3-ones and for the corresponding imines and fulvenes are shown in Table VII. The pyrrolizinones show a reasonably close resemblance to 3*H*-pyrrolizines in their spectra, with the expected downfield shift of H1. This downfield shift is increased by an electron-withdrawing substituent in position 2.<sup>65</sup> Dialkylamino groups in position 1 cause an upfield shift of the signal for H2.<sup>99</sup> In the spectra of 3-hydroxyimino-3*H*-pyrrolizine (**204**)<sup>43</sup> and of the more complex imines of general type **205**,<sup>67,68</sup> the signal for H5 shows a significant downfield shift, although the *N*-ethylimine **206** does not show this effect.<sup>95</sup> A few azafulvenes

have been prepared but show no significant differences from 3*H*-pyrrolizines.<sup>115,120,128</sup>

Few 1*H*-pyrrolizin-1-ones are known, including the parent (23) and a number of 2-substituted derivatives (207).<sup>26</sup> The parent (23) has the signal for H3 at lowest field, a trend accentuated when the substituent at C-2 is electron withdrawing. The spectra of 2-chloro- and 2-bromo-1*H*-pyrrolizin-1-ones were determined in a range of solvents and in the presence of Lewis acids antimony pentachloride and stannic chloride. The major change observed is a downfield shift in the signal due to H7, suggesting protonation or Lewis acid association on the oxygen atom (see Table VIII).



## 5. Other NMR Spectra

McNab has reported <sup>13</sup>C-NMR data for 3*H*-pyrrolizin-3-one without assignment.<sup>66</sup> Quaternary carbon signals are at 165.45 (presumably the carbonyl group) and at 136.75; nonquaternary signals occur at 138.06, 121.82, 118.68, 115.25, and 111.42 ppm.

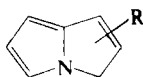
## 6. Mass Spectra

The most common feature of the few published spectra for 3*H*-pyrrolizines is a strong  $M^+$  or  $(M - 1)^+$  peak. The only series of similar compounds where data are available are the ketones 208a–e.<sup>122,123</sup> All show loss of the group R and of the group RCO; either may give the base peak. Phenylthiopyrrolizine 209 has its base peak  $M^+$  and substantial peaks at 180 ( $M - SH$ ) and at 104 ( $M - C_6H_5S$ ).<sup>90</sup>

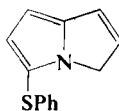
The recorded fragmentation peaks for 3*H*-pyrrolizin-3-one (94a)<sup>66,121</sup> are due to loss of CO and then of HCN. A series of 2-substituted pyrrolizin-3-ones (95a–d) shows fragmentations similar to those of the acylpyrrolizines with loss

<sup>128</sup> M. A. Jessep and D. Leaver, *J.C.S. Perkin I*, 1319 (1980).

of X, COX, and COX + CO.<sup>65</sup> An apparently similar series of 1*H*-pyrrolizin-1-ones shows an interesting difference in fragmentation.<sup>26</sup> The parent (**23**) shows as base peak the molecular ion, followed by loss of acetylene ( $M - 26$ ) and then carbon monoxide. In the substituted 1*H*-pyrrolizin-1-ones (**207**), loss of the substituent predominates, but there are also peaks due to loss of acetylene and of carbon monoxide. In the case of the 2-chloro- and 2-bromopyrrolizinones, there is loss of chloro- and bromoacetylene. There are a few other derivatives of pyrrolizine for which mass spectral data are recorded.<sup>20,64,83,95,120,121</sup>



- (208a) R = 2-Ac  
 (208b) R = 5-Ac  
 (208c) R = 6-Ac  
 (208d) R = 5-CHCl<sub>2</sub>CO  
 (208e) R = 5-CCl<sub>3</sub>CO



(209)

### 7. Miscellaneous Physical Properties

Only one X-ray structure is available for a substituted 3*H*-pyrrolizine.<sup>129</sup> The bond lengths and angles are shown in Fig. 2. Noteworthy are the small angle at N-C-5-C-6 and the greater alternation in bond length in ring A, indicating limited conjugation of the C-1-C-2 double bond with the pyrrole ring.

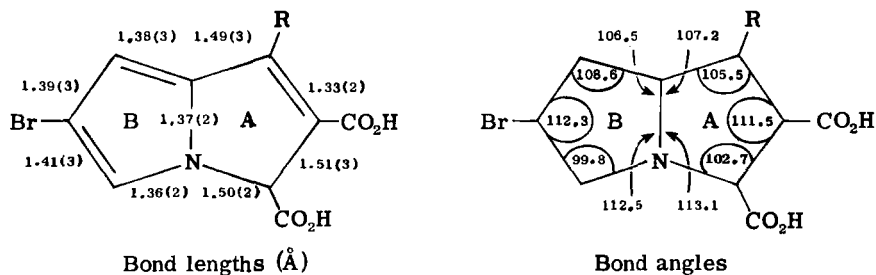


FIG. 2. Bond lengths and bond angles for 6-bromo-1-(*N*-pyrrolidinyl)pyrrolizine-2,3-dicarboxylic acid.

<sup>129</sup> J. L. Flippen and R. D. Gilardi, *Cryst. Struct. Commun.* **3**, 623 (1974).



Okamura and Katz have determined the  $pK_a$  of 3*H*-pyrrolizine by measuring the rate of exchange of its protons with 5 *M* D<sub>2</sub>O in dimethylformamide containing 1 *M* triethylamine.<sup>115</sup> The value of 29 seems surprisingly high compared with those of indene (18.2), cyclopentadiene (15), and fluorene (22.8).

## B. CHEMICAL PROPERTIES

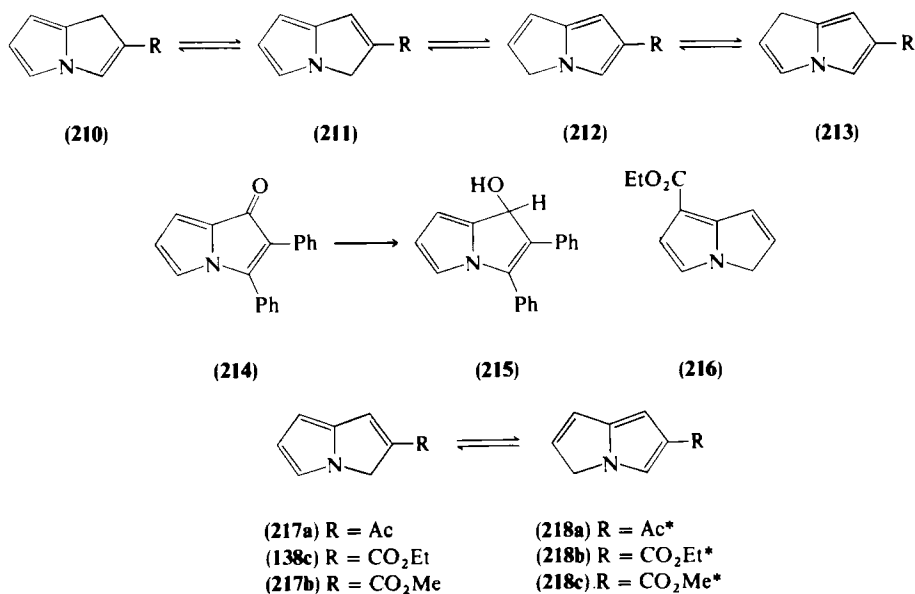
### 1. Tautomerism

The four possible tautomers of a monosubstituted pyrrolizine are shown in structures 210–213. In the unsubstituted 3*H*-pyrrolizine, the 3*H* tautomer (211 or 212) is the only one detectable. There are two major areas of tautomerism that are of particular interest, those represented by equilibria  $211 \rightleftharpoons 212$  and  $210 \rightleftharpoons 211$ . The former is more common. The presence of 1*H*-pyrrolizines in the mixture obtained from the 2-formylpyrrol anion and alkyl- or crotylphosphonium salts was suggested,<sup>70</sup> but no evidence was available to establish which compounds were present. An attempt to prepare 5-methyl-3*H*-pyrrolizine by interaction of the 2-formyl-5-methylpyrrol anion and vinyltriphenylphosphonium bromide also gave a mixture of three isomeric methylpyrrolizines.<sup>83</sup> Evidence from the NMR spectrum of the mixture and from the relative proportions of the two dihydropyrrolizines obtained by reduction of the mixture led to the suggestion that the compounds were the two 3*H* isomers 133a and 133b and the 1*H* isomer 133c in the proportions 10:46:44. This may represent the equilibrium mixture because the reactions were conducted under strongly basic conditions, but it is not clear why 1*H* isomers are formed only when a 3-alkyl substituent is present. Reduction of the 3*H*-pyrrolizin-1-one (214) by lithium aluminum hydride may give the 1-hydroxy-1*H*-pyrrolizine (215), but this structure is not substantiated by NMR data.<sup>40</sup>

Much more common but equally confusing is the 3*H*  $\rightleftharpoons$  5*H* tautomerism, exemplified by equilibrium  $211 \rightleftharpoons 212$ . A number of incorrect assignments occur in the early literature when NMR spectra were not available. In many cases equilibrating conditions were used in the synthesis. Of the 1(7)-substituted pyrrolizines, the methyl derivative certainly has the structure 149<sup>82,120,125</sup>; the compound synthesized from 3,4-dimethyl-2-formylpyrrole, at first thought to be the 6,7-dimethyl compound,<sup>24</sup> is actually the 1,2-dimethyl isomer (130b).<sup>26</sup> Equally certain is the compound synthesized from ethyl 2-pyrrolylglyoxylate, the 7-substituted isomer (216)<sup>123</sup> (1% of an unspe-

cified isomer was said to be present in the crude product). Less certain is the structure of the enol acetate (196) from the dihydropyrrolizin-1-one (3a).<sup>8</sup>

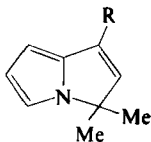
More examples are available when the substituent is in position 2 (6), and the position of the equilibrium between the two tautomeric forms appears to depend on the electron-withdrawing or -donating character of the substituent. Thus 2-methyl- (138a)<sup>119</sup> and 2-phenylpyrrolizine (138b)<sup>87</sup> are the stable forms, the latter showing also unusual chemical stability. On the other hand, 2-pyrrolizinyll ketones and esters are converted under equilibrium conditions to the 6-substituted 3*H*-pyrrolizines. Both 2-benzoyl-3*H*-pyrrolizine (58b) and 6-benzoyl-3*H*-pyrrolizine (58d) were obtained by synthesis under weakly basic conditions,<sup>43</sup> but it is clear that the latter is the more stable isomer. Similarly, 2-acetyl-3*H*-pyrrolizine (217a) was obtained at low temperature under kinetic control, but 6-acetyl-3*H*-pyrrolizine (218a) was the product under equilibration conditions.<sup>122</sup> One of the earliest syntheses of pyrrolizines was reported to give ethyl 3*H*-pyrrolizine-2-carboxylate (138c),<sup>14</sup> but Flitsch and Heidhues showed it to be isomer 218b.<sup>43</sup> A later report<sup>130</sup> of the synthesis of ester 217b was also shown to be in error.<sup>87</sup> The esters 138c and 217b have been isolated and characterized as minor products by Schneckeburger and Vollhardt.<sup>44</sup>



\* More stable isomer

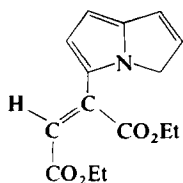
<sup>130</sup> T. Minami, H. Suganuma, and T. Agawa, *Chem. Lett.*, 285 (1978).

The only simple 3-substituted pyrrolizines where tautomerism is not observed are the 3,3-dimethyl derivatives **219a** and **219b**, where a methyl shift would be required.<sup>70,83</sup> Attempts to prepare 3-methyl-,<sup>70</sup> 3-ethyl-,<sup>70</sup> or 5-methyl-3*H*-pyrrolizine<sup>120</sup> led to mixtures (see Section II,A,4). In one synthesis (see Section II,B,2) the two *N*-pyrrylpyrrolizines **145a** and **145c** were obtained in yields of 17 and 8%, respectively, but this may reflect decomposition pathways as much as relative stabilities.<sup>89</sup> The pyrrolizinyl acetates **114a** and **114b**, formed in a base-catalyzed reaction and therefore presumed to be in equilibrium, were estimated to be formed in a ratio of 4:1.<sup>71</sup> From the reaction between 1-methyl-3*H*-pyrrolizine and diethyl acetylenedicarboxylate a 5-pyrrolizinylnmaleate (**220**) was obtained (see Section III,B,4 for further transformation of this compound).<sup>120</sup> The ethylthio- and phenylthio-3*H*-pyrrolizines synthesized by Flitsch and Lubisch<sup>90</sup> were shown to have structures **221**,<sup>123</sup> and the ketones obtained by Friedel-Crafts reactions from 3*H*-pyrrolizine had structures (**222**).<sup>123</sup> Again there appears to be some correlation between electron-withdrawing ability of the substituent and its preference for the pyrrole ring.

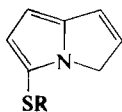


(**219a**) R = H

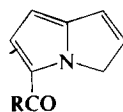
(**219b**) R = Me



(**220**)



(**221**) R = Et, Ph

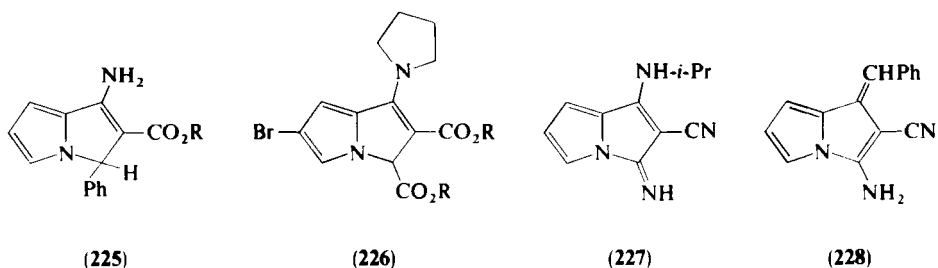
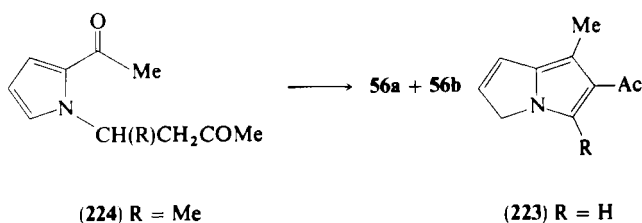


(**222**) R = Me, CHCl<sub>2</sub>, CCl<sub>3</sub>

Di- and polysubstituted pyrrolizines are uncommon. The only pyrrolizine isolated from the intramolecular aldol condensation of 2-acetyl-1-(butan-3-on-1-yl)pyrrole was the 6,7-disubstituted compound **223**.<sup>122</sup> A small amount of the 5,6-disubstituted pyrrolizine (**145d**) was obtained when the 2-formylpyrrol anion was condensed with 1,2-di(phenylsulfonyl)ethene.<sup>90</sup> By contrast with the production of the single isomer (**223**), the homologous diketone **224**

gave a 2:1 mixture of isomers **56a** and **56b**.<sup>42</sup> The polysubstituted pyrrolizines **132**,<sup>43</sup> **225**,<sup>20</sup> and **226**<sup>96</sup> are unique isomers; the structure **226** was confirmed by an X-ray diffraction on the diacid.<sup>129</sup>

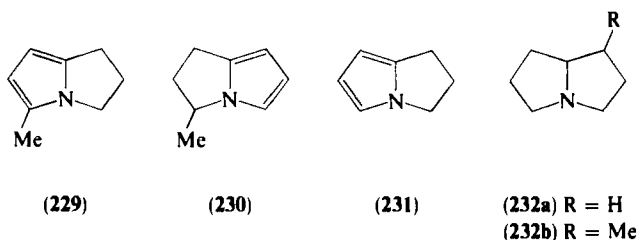
The 1-amino-3*H*-pyrrolizines are potentially tautomeric. Whereas the 1-isopropylamino derivative **227** is reported to have the 3-imino structure, the 1-benzyl derivative is said to favor the 3-amino form (**228**).<sup>67</sup>



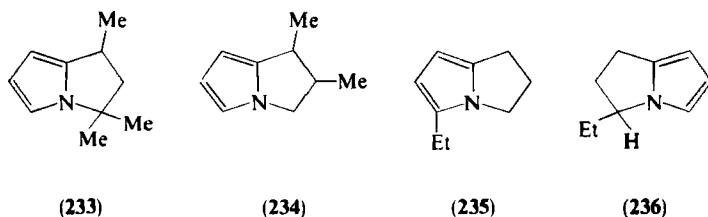
## 2. Reduction and Other Addition Reactions Excluding Cycloaddition

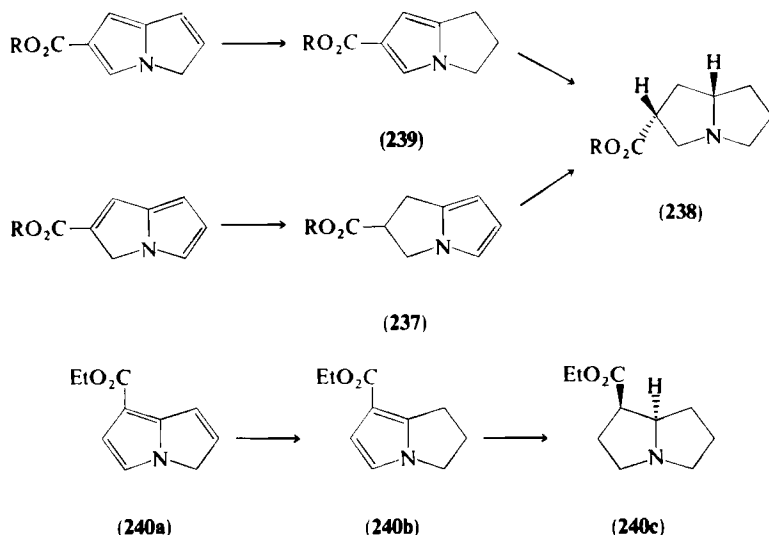
**a. Reduction of the Ring in 1*H*- and 3*H*-Pyrrolizines.** In both series the double bond (1,2 or 2,3) is much more easily reduced than the pyrrole ring, and the isolation of dihydropyrrolizines is easily achieved. This hydrogenation was used to identify the products formed from the 2-formyl-5-methylpyrrol anion and vinyltriphenylphosphonium bromide (see Section II,B,2). Hydrogenation of the mixture, using palladium on charcoal and ether as solvent, gave equal amounts of the two dihydropyrrolizines (**229** and **230**), which could be separated and characterized.<sup>83</sup> From the integrated NMR spectrum of the pyrrolizine mixture and the observation that compounds **229** and **230** were obtained in almost equal proportions, it could be deduced that the pyrrolizines were the isomers **133a-c** in the proportion 46:10:44. The parent 3*H*-pyrrolizine (**1**) can be reduced by hydrogen at atmospheric pressure

and ambient temperature to a dihydro derivative (**231**), and subsequently to a pyrrolizidine (**232a**). In the first report,<sup>14</sup> platinum oxide was the catalyst for both stages, a neutral solvent giving the dihydro derivative (**231**) and glacial acetic acid the pyrrolizidine (**232a**). Subsequently a rhodium-on-carbon catalyst, giving compound **231** in ether and compound **232a** in ethanol,<sup>2,82</sup> was used.

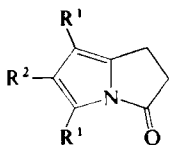
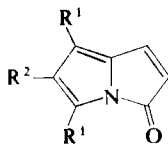


A similar reduction of 1-methyl-3H-pyrrolizine, using ethanol as solvent, gave *dl*-heliotridane **232b**. Other simple pyrrolizines catalytically reduced are 1,3,3-trimethyl-3H-pyrrolizine (rhodium on carbon, methanol)<sup>70</sup> and 1,2-dimethyl-3H-pyrrolizine (palladium on charcoal, ether)<sup>83</sup> to give the dihydro derivatives **233** and **234**, respectively. The latter was particularly important in providing a structure correction; the compound obtained by synthesis from 3,4-dimethyl-2-formylpyrrole<sup>121</sup> had been thought to be 6,7-dimethyl-3H-pyrrolizine, but the NMR spectrum of the dihydro derivative (**234**) showed that the methyl groups were on the saturated ring. Other mixtures obtained from pyrrolizine synthesis have been reduced, in one case giving compounds **229** and **230**,<sup>70</sup> in another the 3-ethyl derivatives **235** and **236**,<sup>70</sup> but in neither case was it possible to estimate the proportions of isomers. Reduction of some pyrrolizines has been used to provide routes to pyrrolizidines. Reduction of the pyrrolizine-2- or -6-carboxylates gave dihydro derivatives **237** and **239** (rhodium on alumina, methanol), or the pyrrolizidine ester **238** (rhodium on alumina, aqueous acetic acid).<sup>44</sup> The isolation of a single stereoisomer is particularly noteworthy. Ethyl ester (**240a**) also gives on reduction a dihydro derivative (**240b**) or a predominant diastereomer (**240c**) of the pyrrolizidine ester.<sup>123</sup>

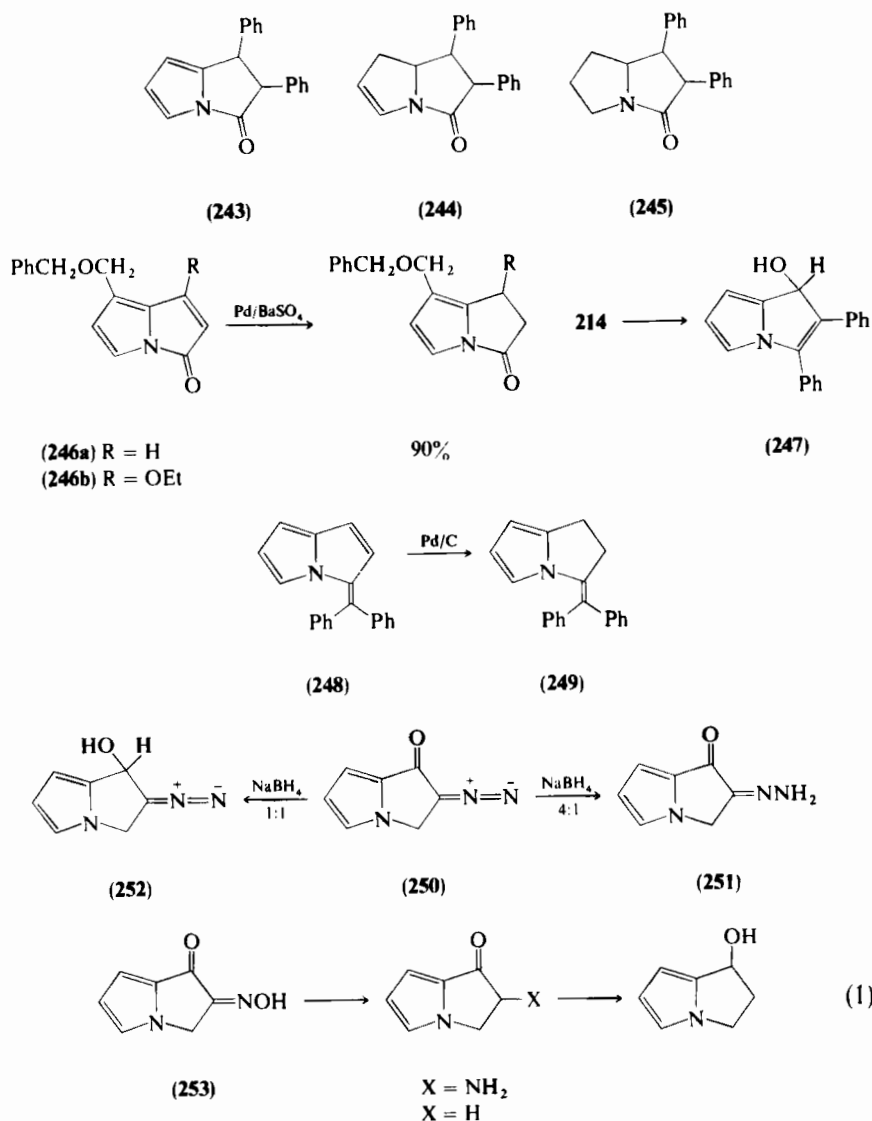




b. *Nuclear Reduction of Pyrrolizinones and Azafulvenes.* The reduction of 3*H*-pyrrolizin-3-one (94a), using palladium on charcoal, gives the dihydro derivative (241),<sup>39</sup> and the trisubstituted 3*H*-pyrrolizin-3-one (242) yields a dihydro derivative,<sup>63</sup> but the diphenyl-3*H*-pyrrolizin-3-one (52b) forms a mixture of dihydro- (243) and tetrahydro- (244) derivatives when reduced in ethanol in the presence of the Adams catalyst.<sup>131</sup> Reduction in acetic acid with the same catalyst converted the pyrrolizinone (52b) or the mixture of partially reduced materials to the pyrrolizidinone (245) of undetermined stereochemistry.<sup>131</sup> The benzyloxymethylpyrrolizinones (246a,b) give 1,2-dihydropyrrolizinones on reduction.<sup>64,93</sup> Reduction of 2,3-diphenyl-1*H*-pyrrolizin-1-one (214) by lithium aluminum hydride leads to the 1-hydroxy-1*H*-pyrrolizine (247)<sup>40</sup>; there are no other reports of isolated stable 1*H*-pyrrolizines. The azafulvene (248) was reduced to the dihydro derivative (249).<sup>43</sup>

(241)  $\text{R}^1 = \text{R}^2 = \text{H}$ , 80%(242)  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{CO}_2\text{Et}$ 

<sup>131</sup> V. Carelli, M. Cardellini, and F. Morlacchi, *Ann. Chim. (Rome)* **51**, 604 (1961) [*CA* **56**, 5912 (1962)].

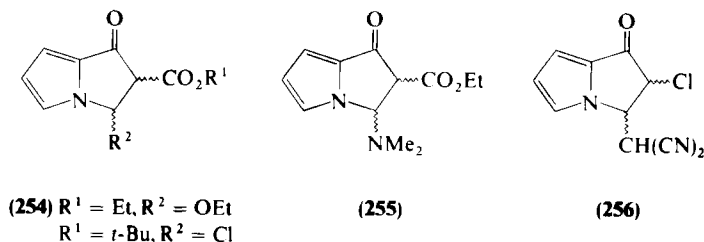


Reduction of 2-diazo-3*H*-pyrrolizin-1-one (**250**) by borohydride can take two routes, depending on the relative proportions of hydride and pyrrolizinone, to give either the 1-hydroxy derivative (**252**) or the hydrazone (**251**).<sup>132</sup> A much more exhaustive study has been made of the electrochemical

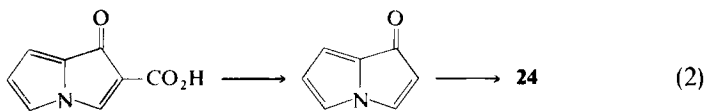
<sup>132</sup> M. Cardellini, V. Carelli, F. Liberatore, and F. Morlacchi, *Chim. Ind. (Milan)* **50**, 455 (1968) [*CA* **69**, 77040 (1968)].

reduction of the pyrrolizin-1,2-dione monoxime (**253**).<sup>133</sup> The final product is 1-hydroxy-1,2-dihydro-3*H*-pyrrolizine; the stages are summarized in Eq. (1).

c. *Other Addition Reactions.* The only simple addition reactions are those of 1*H*-pyrrolizin-1-ones.<sup>26</sup> Those pyrrolizin-1-ones that contain an electron-withdrawing group at position 2 readily accept alcohols or dimethylamine by addition to give **254** or **255**.<sup>26</sup> More remarkably, 2-chlorocarbonylpyrrolizin-1-one reacts with chlorine or with bromine in an addition-elimination reaction giving 2-chloro- (**21a**) or 2-bromo- (**201**, R = Br) pyrrolizinones.<sup>26</sup> The chloro compound (**21a**) also is reported to react with malononitrile by addition, giving **256**, although the chemical shift assigned to H3 (6.22 ppm) seems hard to justify.



Decarboxylation of the pyrrolizinone-2-carboxylic acid gives very little of the parent pyrrolizinone; instead **24** is produced when the anionic intermediate, formed on decarboxylation, adds in a Michael manner to the pyrrolizinone<sup>26</sup> [Eq. (2)].



### 3. Oxidation

Although alkylpyrrolizines are very unstable in air at room temperature, there are no reports of controlled oxidation of pyrrolizines or pyrrolizinones. The oxime from 3*H*-pyrrolizine-1,2-dione (**253**) has been oxidatively aminated by chloramine to the diazoketone (**250**).<sup>134</sup>

<sup>133</sup> M. Cardinali, *J. Electroanal. Chem. Interfacial Electrochem.* **42**, 49 (1973) [*CA* **78**, 143172 (1973)].

<sup>134</sup> F. Morlacchi and M. Cardellini, *Ann. Chim. (Rome)* **57**, 260 (1967) [*CA* **67**, 53965 (1967)].

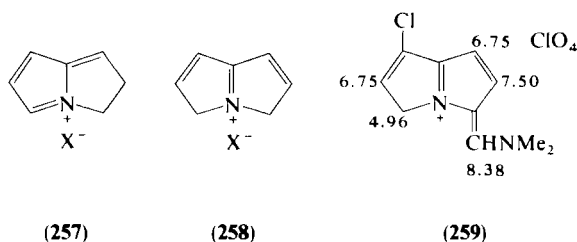


#### 4. Reaction with Electrophiles

The formal similarity of 3*H*-pyrrolizines to vinylpyrroles leads to an expectation of high reactivity toward electrophiles, but this has seldom been translated into synthetically useful processes.

The protonation of 3*H*-pyrrolizines has been studied by Flitsch and Heidhues<sup>43</sup> after their discovery that 2-benzoyl-3*H*-pyrrolizine is easily converted to the 6-substituted isomer by mineral acids. Pyrrolizines are generally unstable in dilute acid, but they can be dissolved in concentrated sulfuric acid and subsequently recovered. The protonation was studied by <sup>1</sup>H-NMR spectroscopy. Protonation occurs at C-2 and C-5 to give a mixture of pyrrolizinium salts [**257** (45%) and **258** (55%)]. The proportions are slightly different for protonation of 1-methyl-3*H*-pyrrolizine (C-2 to C-5 = 35:65), and the highly substituted compound **132** is protonated exclusively at C-2. The chemical shifts of 3*H*-pyrrolizine (**1**) and of its two protonated forms (**257** and **258**) are given in Table IX. Protonation of 3*H*-pyrrolizin-3-one gives an unstable species having a low-lying LUMO.<sup>42</sup>

Protonation of 1*H*-pyrrolizin-1-ones appears to take place on oxygen (see Sections III,A,2 and III,A,4). The other derivative of type **258** is the Vilsmeier formylation intermediate from 1-chloro-3*H*-pyrrolizine, the perchlorate



$$J_{1,2} = 5 \text{ Hz}$$

$$J_{5,6} = 2 \text{ Hz}$$

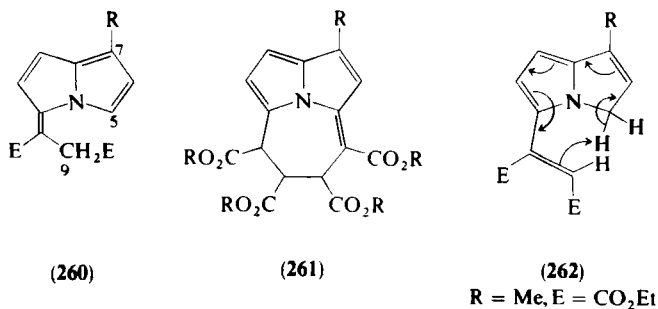
TABLE IX  
<sup>1</sup>H-NMR DATA FOR 3*H*-PYRROLIZINE AND ITS PROTONATED FORMS<sup>a</sup>

Compound	Solvent	Chemical shifts						<i>J</i> values (Hz)
		H1	H2	H3	H5	H6	H7	
<b>1</b>	CS <sub>2</sub>	6.44	5.72	4.27	7.70	6.00	6.00	
<b>257</b>	H <sub>2</sub> SO <sub>4</sub>	7.2	4.1	4.98	7.93	6.85	7.38	<i>J</i> <sub>1,2</sub> = 4.0
<b>258</b>	H <sub>2</sub> SO <sub>4</sub>	7.08	7.93	4.97	4.97	7.93	7.08	<i>J</i> <sub>1,2</sub> = 5.5

<sup>a</sup> Data from ref. 43.

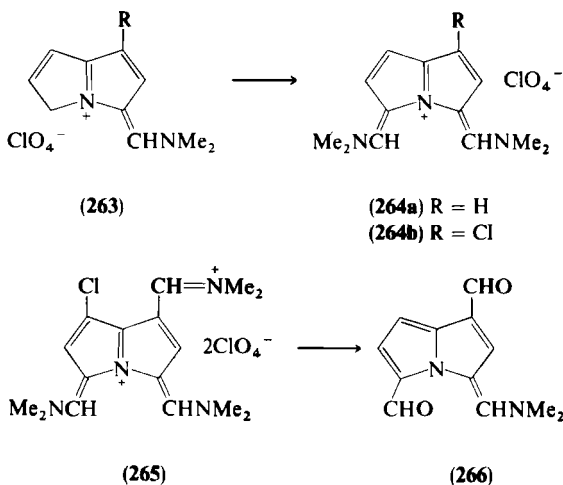
**259.**<sup>67</sup> The chemical shifts are shown with the formula, and the compound has  $\lambda_{\max}$  206 (3.96), 241 (4.06), and 377 nm (5.27). Other derivatives of the 3*H*,5*H*-pyrrolizinium ion are the bis- and trisdimethylaminomethylene salts described later in this section.

The most consistently successful electrophilic substitutions have been those where a subsequent hydrogen shift converts a 3*H*-pyrrolizine to an azafulvene. From the reaction between 3*H*-pyrrolizines and acetylenedicarboxylates two series of products were obtained, the azafulvenes (**260**)<sup>120</sup> and the cyclazine derivatives (**261**).<sup>121</sup> The latter are dealt with in Section III,B,6. By a combination of labeling with deuterium at H3 and by use of alkyl-substituted pyrrolizines the mechanism was established.<sup>120</sup> When 1-methyl-3*H*-pyrrolizine was used, the methyl group in the product was at position 7. When 3-deuterio-3*H*-pyrrolizine was used and chromatography avoided in the workup, the product had 50% <sup>2</sup>H content at position 5 and 25% <sup>2</sup>H (= 0.5 <sup>2</sup>H) at position 9, indicating that the hydrogen-transfer step is intramolecular, probably a 1,9-sigmatropic shift. Chromatography of this deuterated product resulted in loss of the <sup>2</sup>H from position 9. Finally 1-methyl-3*H*-pyrrolizine reacted slowly with diethyl acetylenedicarboxylate to give a compound (**262**) that could be converted by further heating to the azafulvene, thus establishing it as a probable intermediate. Other acetylenes (propiolate, diphenylacetylene, dicyanoacetylene) either failed to react or gave unidentified products.

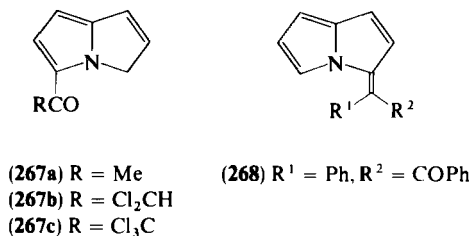


Vilsmeier formylation has attracted much attention as a route to cyclazines (see Section III,B,6). Jessep and Leaver have obtained the Vilsmeier salt **263** from **1** by using dimethylformamide and phosphoryl chloride at  $-65^{\circ}\text{C}$ , but the formylpyrrolizine was very unstable, and a second Vilsmeier reaction has not been achieved.<sup>128</sup> The salt **263** could be converted to the 3,5-bisaldehyde equivalent **264a** by treatment with dimethylthioformamide and acetic anhydride. Flitsch *et al.* prepared 1-chloro-3*H*-pyrrolizine and treated it *in situ* at  $-60^{\circ}\text{C}$  with the Vilsmeier reagent to obtain the chloro derivative **259** of compound **263**.<sup>67</sup> They also obtained the bis(dimethylaminomethylene) derivative **264b** and, at room temperature, the tris(dimethylaminomethylene) derivative **265**, which was hydrolyzed to give the dialdehyde **266**. Reactions

involving vinylamidinium salts are probably electrophilic substitutions, but the products are cyclazines, and the reactions are dealt with in Section III,B,6.

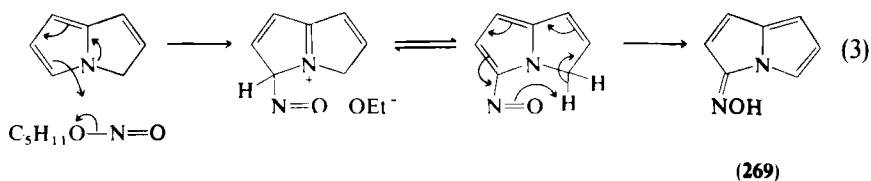


The other major examples of electrophilic substitution on 3*H*-pyrrolizine (1) are Friedel–Crafts acylations. Jones and Radley, during attempts to add dichloroketene to pyrrolizine, discovered that the major products were 5-acetyl- (267a), 5-dichloroacetyl- (267b), and 5-trichloroacetylpyrrolizine (267c), depending on the reagent used.<sup>123</sup> Compounds 267b and 267c could be prepared in good yield by reaction between 3*H*-pyrrolizine, the appropriate acid chloride, and anhydrous potassium carbonate, in ether, but the 5-acetyl derivative could not be obtained in this manner. Reduction of the trichloroacetyl derivative 267c by zinc and acetic acid gave the 5-acetyl derivative 267a.

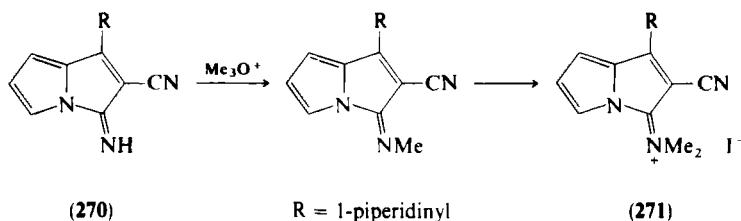


Not surprisingly, the anion derived from 3*H*-pyrrolizine is a stronger nucleophile than compound 1 itself. Thus the anion reacts with deuterium oxide to give 3<sup>1</sup>*H*,3<sup>2</sup>*H*-pyrrolizine, but attempts at further enrichment give mixed deuteriopyrrolizines.<sup>83,115</sup> The anion reacts with ketones to give azafulvenes such as 248 and 268.<sup>43,115</sup> It seems possible that the reported formation of the oxime of 3*H*-pyrrolizine-3-one (269) from 3*H*-pyrrolizine and

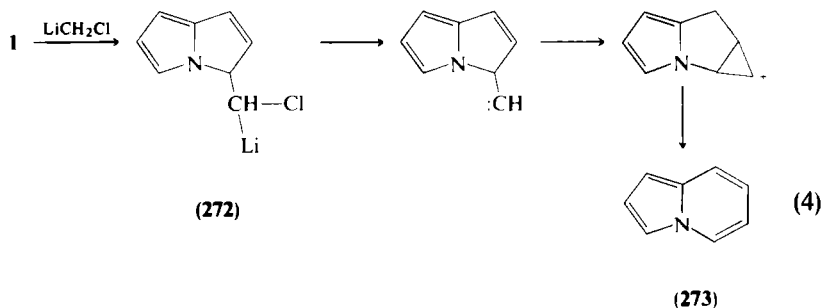
amyl nitrite<sup>43</sup> is an electrophilic substitution [Eq. (3)]. The suggestion that it proceeded via the anion seems at variance with the high  $pK_a$  value of 3*H*-pyrrolizine.



The addition-elimination reaction between 2-chlorocarbonyl-1*H*-pyrrolizin-1-one and chlorine has been described (see Section III,B,2,c). The 2,5-dichloro derivative **21b** isolated in the same reaction must presumably be derived from an electrophilic substitution on the initially formed 2-chloropyrrolizinone.<sup>26</sup> The iminopyrrolizine **270** can be methylated, first with Meerwein's reagent and then by methyl iodide to give the quaternary salt **271**, which reacts readily with nucleophiles (see Section III,B,5).



The only reaction reported between 3*H*-pyrrolizine (**1**) and a carbene (or carbenoid) is that involving *n*-butyllithium and dichloromethane.<sup>135</sup> One of the products is formed by cycloaddition (Section III,B,6), one by ring opening (Section III,B,7), and the third according to Eq. (4). The latter two products are viewed as derived from the carbenoid **272**, and the proposed route to indolizine (**273**) is shown in Eq. (4).



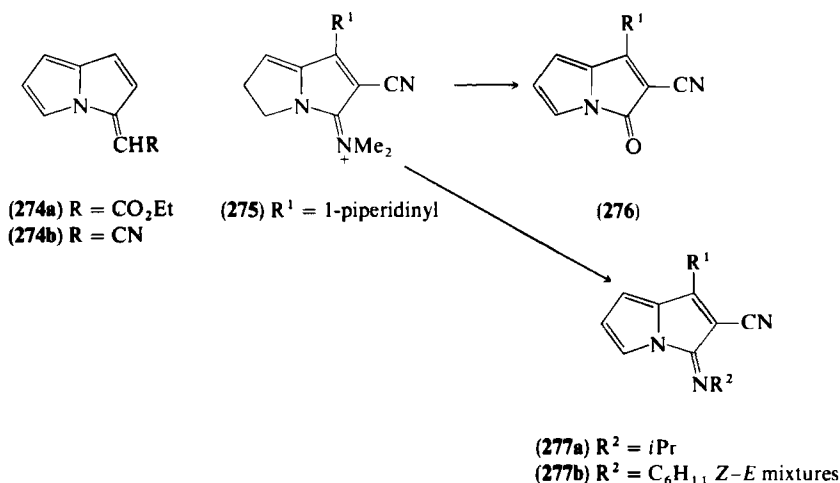
<sup>135</sup> U. Burger and F. Dreier, *Helv. Chim. Acta* **62**, 540 (1979).

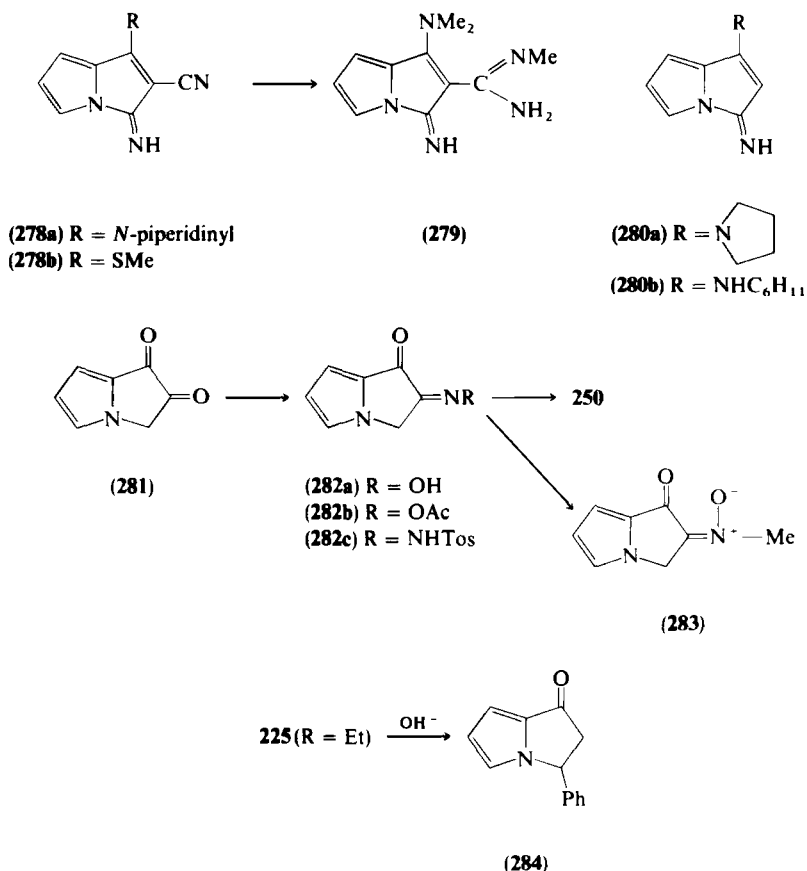
### 5. Reactions with Nucleophiles

There are no reports of substitution reactions between simple 3*H*-pyrrolizines and nucleophiles (deprotonation is mentioned in Section III,A,4 and the reactions of the anion in Section III,B,4). The pyrrolizinones, as expected, are more reactive toward nucleophiles. Some nucleophiles add to the 2,3-bond of 1*H*-pyrrolizin-1-ones (see Section III,B,2); similar reactivity is not reported for 3*H*-pyrrolizin-3-ones. Thus acid chloride **95a** reacts with water to give acid **95b**, with ethanol to give ester **95c**, and with diethylamine to give amide **95d**.<sup>65</sup> Many reactions at the ring carbonyl group lead to ring opening (Section III,B,7), but a few lead to tricyclic products. Reduction of the 1*H*-pyrrolizin-1-one (**214**) by lithium aluminium hydride<sup>40,135</sup> has been mentioned (Section III,B,2) as has reduction of diazoketone **250**.<sup>133</sup> Successful Wittig reactions have been reported for 3*H*-pyrrolizin-3-one, giving the azafulvenes **274a,b**.<sup>39,71</sup>

The dimethyliminopyrrolizinium salt **275** has been hydrolyzed to the pyrrolizinone **276** by base and converted to a mixture of *Z* and *E* imines **277a** or **277b** by primary amines.<sup>67</sup> On the other hand, the 1*H*-pyrrolizinium salt **8** is reported to give a carbinolamine (**11**) when treated with water.<sup>19</sup> Imine **278a** reacted with dimethylamine in ethanol to give a product (**279**) in which nucleophilic substitution appears to have taken place.<sup>67</sup> The similar 1-methylthiopyrrolizinimine (**278b**), which has a better leaving group, reacts with pyrrolidine, with cyclohexylamine, or with isopropylamine to give the 1-aminopyrrolizinimines **280a**, **280b**, and **227**.<sup>67</sup>

Diketopyrrolizine **281** can be converted to a number of derivatives of the C-2 carbonyl group; these include the oxime (**282a**), the acetate (**282b**), and the tosylhydrazone (**282c**). From the oxime (**282a**), a series of derivatives of the





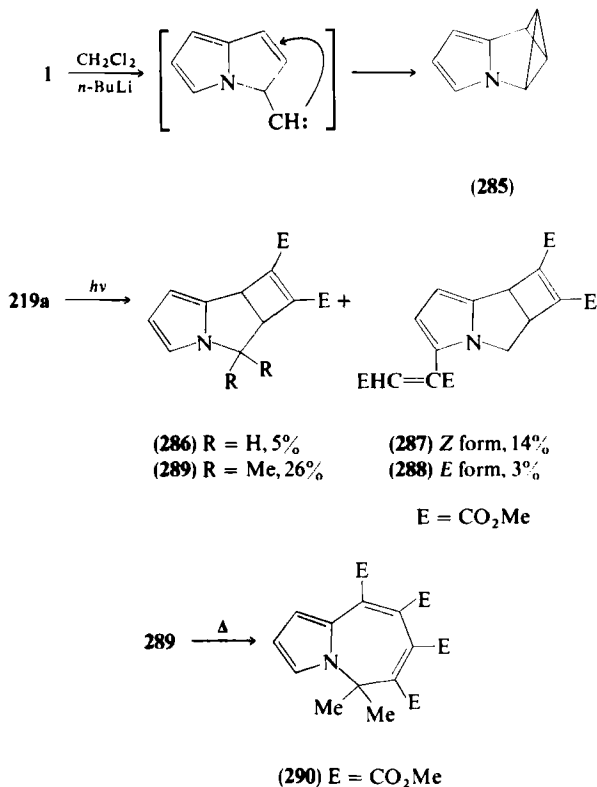
C-1 carbonyl group were obtained<sup>136</sup> and from the tosylhydrazone (282c) or the oxime (282a) a diazoketone (250).<sup>136</sup> Methylation of the oxime (282a) gave a nitron (283). Hydrolysis of the 1-aminopyrrolizine-2-carboxylate (225) gave the dihydropyrrolizinone (284).<sup>20</sup> Hydrolysis of ethyl 3*H*-pyrrolizin-2-carboxylate gave the acid, decarboxylated to provide a synthesis of 3*H*-pyrrolizine.<sup>14</sup>

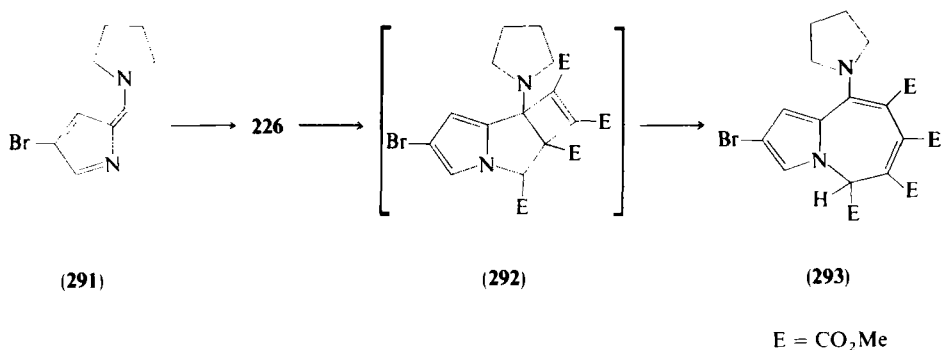
## 6. Cycloaddition Reactions and Cyclization to Give Extra Fused Rings

The known cycloaddition reactions of 3*H*-pyrrolizines and of pyrrolizinones involve only one double bond in the molecule; azafulvenes and

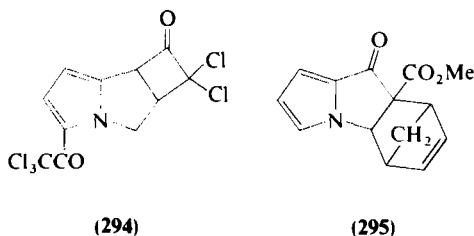
<sup>136</sup> V. Carelli, M. Cardellini, and F. Morlacchi, *Ann. Chim. (Rome)* **57**, 1462 (1967) [*CA* **69**, 2794 (1968)].

pyrrolizinimines can act as  $8\pi$ -electron components in the formation of a new ring linking C-3 to C-5. A carbene addition to 3*H*-pyrrolizine gives as one product the compound **285**, the intermediate 3-pyrrolizinyl carbene adding to the C-1–C-2 bond.<sup>135</sup> Photochemical ( $2\pi + 2\pi$ ) additions have been studied by Johnson and Jones.<sup>83</sup> The parent 3*H*-pyrrolizine (**1**) reacted very rapidly with acetylenedicarboxylates in a thermal reaction (see Section III,B,4) so that photochemical addition was unfavorable, but it was possible to isolate the ( $2\pi + 2\pi$ ) adduct **286** (5%) and also the more complex addition products **287** (14%) and **288** (3%). From 3,3-dimethyl-3*H*-pyrrolizine (**219a**), in which the thermal reaction is slow because of hindrance at C-5, it was possible to obtain a better yield (26%) of a ( $2\pi + 2\pi$ ) adduct (**289**), which on heating gave a pyrroloazepine (**290**).<sup>83</sup> This last observation throws some light on the reaction between the azafulvene **291** and dimethyl acetylenedicarboxylate, which gives a pyrrolizine (**226**)<sup>96,129</sup>; this enamino ester must react with a further molecule of acetylenedicarboxylate by addition to give intermediate **292** because the second characterized product was a pyrroloazepine (**293**).<sup>96</sup>





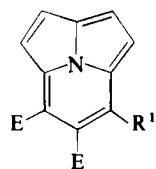
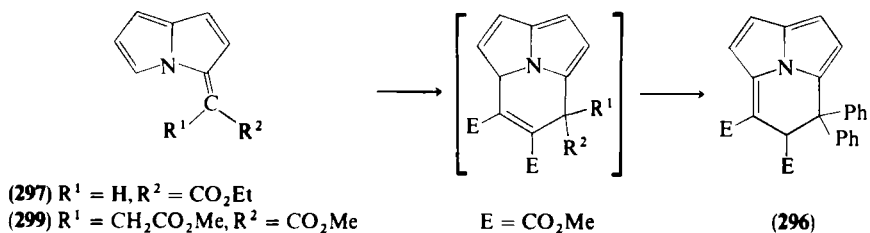
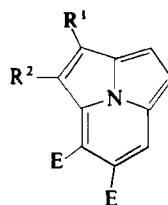
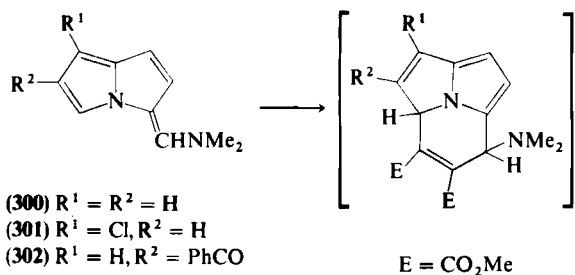
Attempts to add dichloroketene to 3*H*-pyrrolizine (1) were largely unsuccessful, giving Friedel–Crafts products (Section III,B,4); but in one case, in which the ketene was generated from trichloroacetyl chloride and activated zinc in ether, an adduct (294) (or its regioisomer) was obtained.<sup>123</sup> The double bond in the 1*H*-pyrrolizin-1-one can act as a dienophile with cyclopentadiene; ester 295 was isolated.<sup>26</sup>



Some of the azafulvenes formally derived from 3*H*-pyrrolizin-3-one can react with acetylenes to give cyclazines, in a ( $8\pi + 2\pi$ ) cycloaddition. Some activation at the exocyclic double bond seems to be necessary. The diphenyl derivative 248 reacted rapidly with acetylenedicarboxylate to give the cyclazine 296 (after a hydrogen shift<sup>120</sup>); ester 297 reacted more slowly to give cyclazine 298,<sup>83</sup> but ester 299 failed to react under the same conditions.<sup>120</sup> The dimethylamino derivatives 300–302 reacted with dimethyl acetylenedicarboxylate to give the fully delocalized [2.2.3]cyclazines 303–305, elimination of dimethylamine providing the final unsaturation.<sup>67,128</sup>

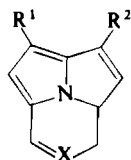
The pyrrolizinium salts 264a,<sup>128</sup> 264b,<sup>67</sup> and 265<sup>67</sup> have been cyclized by aqueous ammonia to give the [2.2.3]cyclazines 306–308. Compound 264a also reacted with nitromethane and potassium *t*-butoxide to give the nitro[2.2.3]cyclazine 309.<sup>128</sup> [2.2.3]Cyclazines 313–315 can also be made from 3*H*-pyrrolizines and the vinylamidinium salts 311 and 312.<sup>87</sup> Cyclazine



(298)  $R^1 = CO_2Et$ 

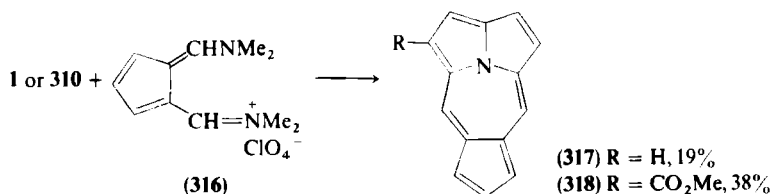
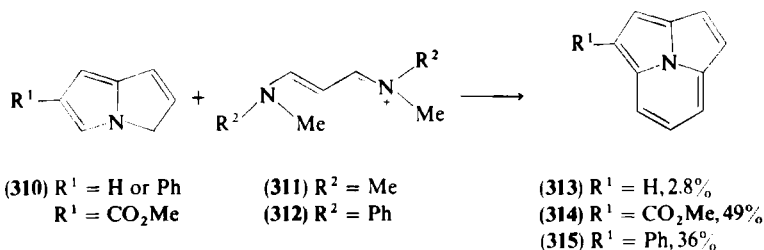
(303)  $R^1 = R^2 = H, 68\%$   
 (304)  $R^1 = Cl, R^2 = H, 32\%$   
 (305)  $R^1 = H, R^2 = PhCO, 12\%$

**314** can also be made from the pyrrolizine-6-carboxylate **310** and malondialdehyde diacetal.<sup>87</sup> The more complex salt **316** from cyclopentadiene reacts with pyrrolizine (**1**) or ester **310** to give the tetracyclic compounds **317**<sup>137</sup> and **318**.<sup>87</sup>



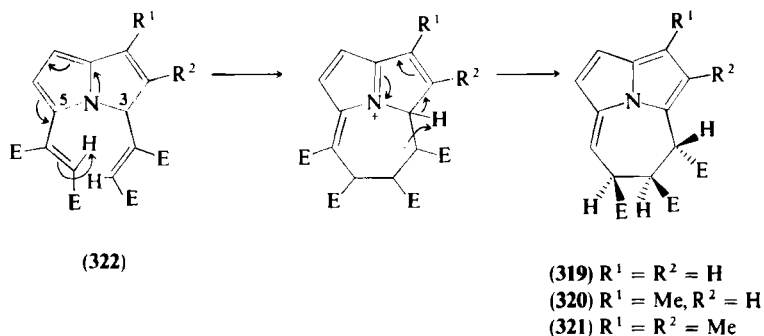
(306)  $R^1 = R^2 = H, X = N, 39\%$   
 (307)  $R^1 = Cl, R^2 = H, X = N, 52\%$   
 (308)  $R^1 = Cl, R^2 = CHO, X = N, 14\%$   
 (309)  $R^1 = R^2 = H, X = C-NO_2, 55\%$

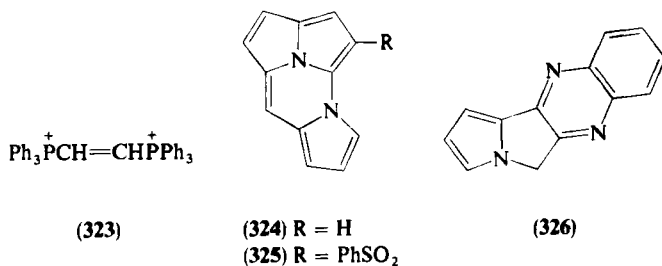
<sup>137</sup> M. A. Jessep and D. Leaver, *J.C.S. Perkin I*, 1324 (1980).



There are two examples of cyclazine formation by formation of a single bond. First, when 3*H*-pyrrolizines react with acetylenedicarboxylates in a ratio of 1:2, the [2.2.4]cyclazine derivatives **319–321** are formed.<sup>121</sup> From a dimethylpyrrolizine (incorrectly thought to be 6,7-dimethyl-3*H*-pyrrolizine) and dimethyl acetylenedicarboxylate a compound (**322**) was isolated, which could be slowly converted by further heating to the cyclazine **321**. Second, cyclization of 3-(2-formyl-1-pyrrolyl)pyrrolizine (**145c**) was achieved by treatment with potassium *t*-butoxide, giving the 5-aza[2.2.3]cyclazine **324**, which could also be obtained directly from the 2-formylpyrrolyl anion and the bisphosphonium salt **323**.<sup>89</sup> A similar mechanism is proposed for the preparation of cyclazine **325** from **141** ( $X = Y = \text{SO}_2\text{Ph}$ ).<sup>90</sup>

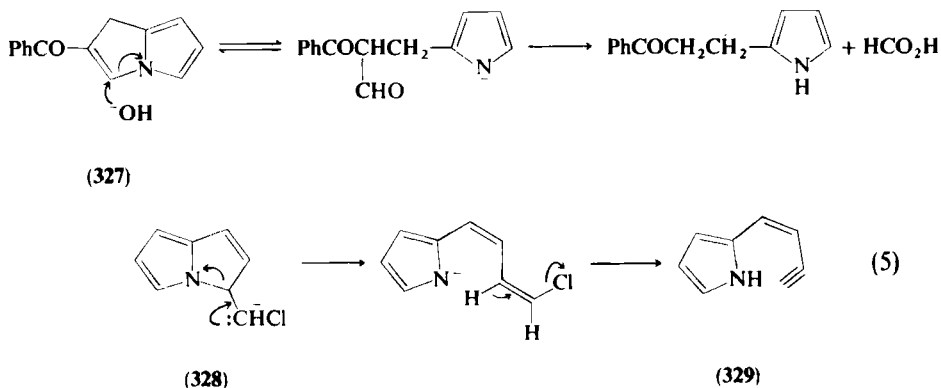
The pyrrolizine diketone **281** reacted with 1,2-diaminobenzene to give the polycycle **326**.<sup>136</sup>



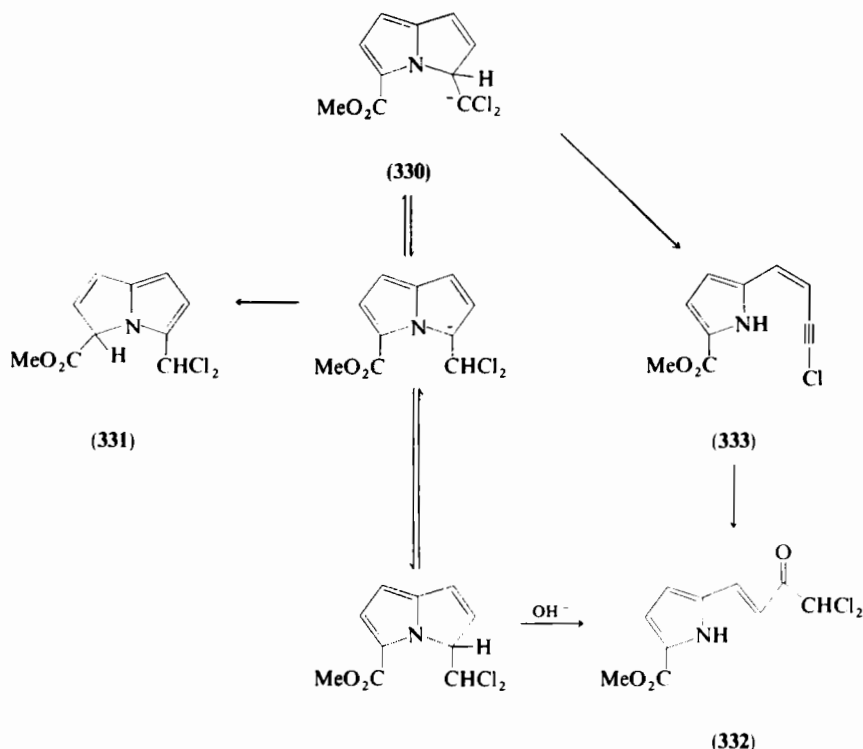


### 7. Reactions Involving Opening of One Ring

There are only three reports of reactions in which one of the rings of a 3*H*-pyrrolizine is opened, excluding ring expansions previously mentioned. The benzoylpyrrolizines **58b** and **58d** are converted by dilute aqueous sodium hydroxide to 1-phenyl-3-(2-pyrryl)propan-1-one.<sup>43</sup> Both pyrrolizines isomerize to a 1*H* isomer (**327**), which is the enamine of a  $\beta$ -diketone, and this is hydrolyzed to give the propanone and formic acid. Reaction between 3*H*-pyrrolizine (**1**) and a lithium dichlorocarbene species in tetrahydrofuran gave indolizine (Section III,B,4), an insertion product (Section III,B,6), and the butenyne **329**.<sup>135</sup> In the mechanism proposed for the formation of **329** [Eq. (5)], the essential feature is the existence of intermediate **328** as an anion



rather than a carbene. Such an anion appears essential to allow cleavage of the C-3–C-4 bond. Jones and Radley have reported<sup>124</sup> that attempts to convert the trichloroacetylpyrrolizine **267c** to a methyl ester by the standard pyrrole method of treatment with anhydrous potassium carbonate in methanol gave two products. One was the bicyclic product **331** that could be converted by further treatment with anhydrous potassium carbonate in methanol to the monocyclic product **332**. The proposed mechanism, shown in Scheme 13,

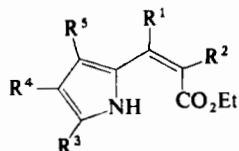


SCHEME 13

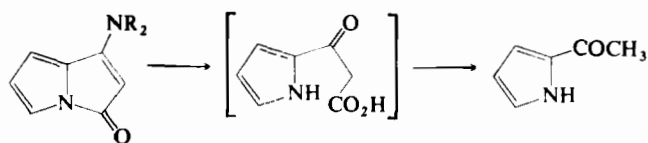
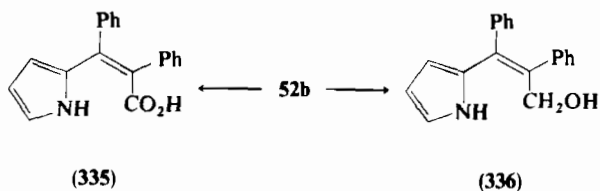
passes through an anion (330) similar to the crucial intermediate (328) described above. A 1,2-hydrogen shift can lead to an equilibrating ion from which the two products can be reached. Protonation of one form gives the bicyclic product 331, whereas protonation of the other leaves the molecule open to nucleophilic attack with the pyrrol anion as leaving group. It is possible to envisage ring opening from 330 to give a chloroenyne (333) with subsequent hydration but this appears less likely in view of the conversion of compound 331 to 332. The absence of any indolizine seems to rule out the involvement of a carbene.

Pyrrolizinsones can react with nucleophiles with opening of the carbonyl-containing ring. The 3*H*-pyrrolizin-3-ones (94a, 242) react with sodium ethoxide in ethanol to give the (*Z*)-2-pyrrolacrylates (334).<sup>39,63</sup> Hydrolysis of 2,3-diphenyl-3*H*-pyrrolizin-3-one (52b) by dilute aqueous sodium hydroxide gave the 2-pyrrolacrylic acid 335,<sup>40</sup> whereas with sodium borohydride it gave the allyl alcohol 336.<sup>132</sup> On the other hand, 1-dialkylamino-3*H*-pyrrolizin-3-ones (337) were reported to be stable to sodium ethoxide but

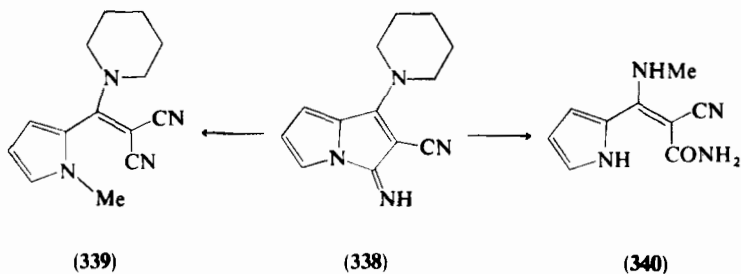
hydrolyzed by dilute aqueous acid or alkali to 2-acetylpyrrole, presumably via the  $\beta$ -keto acids, which decarboxylate.<sup>99,100</sup> The 3*H*-pyrrolizinimine **338** reacted with methyl iodide or with methylamine in an aqueous medium to give pyrroles **339** and **340**, respectively.<sup>67</sup>



	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	Yield (%)
	H	H	H	H	H	63
(334)	Me	H	H	H	H	85
	H	Ph	H	H	H	84
	H	H	Me	CO <sub>2</sub> Et	Me	50



(337) R = Me or Et



# Chemistry of Arene Oxides

G. S. SHIRWAIKER AND M. V. BHATT

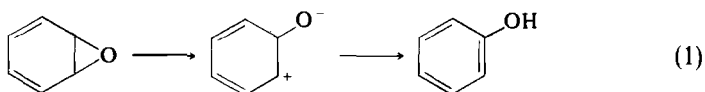
*Department of Organic Chemistry,  
Indian Institute of Science,  
Bangalore, India*

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## I. Introduction

Arene oxides are an important group of labile organic compounds whose chemistry and role in biological processes have come to assume a great deal of interest for the past 15 years. Although they possess a strained oxirane ring, the most important pattern of their reactivity arises from their  $4\pi + 2\sigma$  system. This six-electron system makes them highly susceptible for aromatization to give the isomeric phenolic derivatives [Eq. (1)]. In fact, this reaction takes place spontaneously and also under water and acid catalysis. A second feature, particularly in the case of monocyclic derivatives, is the operation of a dynamic valence tautomerism [Eq. (2)].



The main focus of interest in arene oxides, however, has been their formation and role under biological conditions. There are a number of reviews.<sup>1-8</sup> Every attempt has been made in this article to cover the literature

<sup>1</sup> D. M. Jerina, H. Yagi, and J. W. Daly, *Heterocycles* **1**, 267 (1973).

<sup>2</sup> T. C. Bruice and P. Y. Bruice, *Acc. Chem. Res.* **9**, 378 (1976).

<sup>3</sup> S. C. Agarwal, D. Van, and L. Benjamin, *Carcinog.-Compr. Surv.* **3**, 109-114 (1978) [*CA* **89**, 146793 (1978)].

<sup>4</sup> R. G. Harvey and P. P. Fu, in "Polycyclic Hydrocarbons and Cancer" (H. V. Gelboin and P. O. P. Tsó, eds.), p. 133. Academic Press, New York, 1978.

<sup>5</sup> Anonymous, *Nachr. Chem., Tech. Lab.* **27**, 94 (1979) [*CA* **91**, 20350 (1979)].

<sup>6</sup> D. M. Jerina and J. W. Daly, *Science* **185**, 573 (1974).

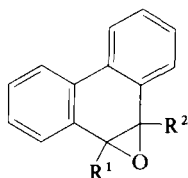
up to the end of 1982. Some biochemistry of arene oxides is included to maintain perspective.

## II. Synthesis of Arene Oxides

### A. DIRECT EPOXIDATION

#### 1. With *m*-Chloroperbenzoic Acid

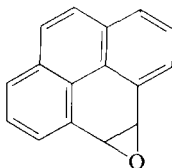
Epoxidation of aromatic hydrocarbons is an important method for the preparation of arene oxides. *m*-Chloroperbenzoic acid (MCPBA) is used in a two-phase system that involves treating the hydrocarbon with a large excess ( $\sim 10$ -fold) of MCPBA in methylene chloride–aqueous sodium bicarbonate at room temperature. The yields are moderate (10–60%). Because the arene oxides are sensitive to acids, the presence of sodium bicarbonate buffer is necessary. A number of K-region (see Section VII for a definition) epoxides like phenanthrene 9,10-oxide (**1**, 59%), 9,10-dimethylphenanthrene 9,10-oxide (**2**, 40%), 9-phenylphenanthrene 9,10-epoxide (**3**, 50%), pyrene 4,5-oxide (**4**, 14%), and chrysene 4,5-oxide (**5**, 9%) have been prepared by this method.<sup>9</sup>



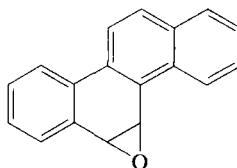
(1)  $R^1 = R^2 = H$

(2)  $R^1 = R^2 = CH_3$

(3)  $R^1 = H; R^2 = Ph$



(4)



(5)

Even the 1,2-dihydrodiol derivatives of polycyclic aromatic hydrocarbons are converted to the corresponding epoxydiols with MCPBA. The reaction is stereoselective only in some cases. The *trans*-dihydrodiols (**6**) give the *anti*-epoxide (**7**), whereas the *cis*-dihydrodiols (**8**) give a mixture of *anti*- (**9**) and *syn*-epoxy compounds (**10**). The *anti*- and *syn*-diol epoxides of benz[*a*]anthracene and benzo[*a*]pyrene have been prepared by this method.<sup>10</sup>

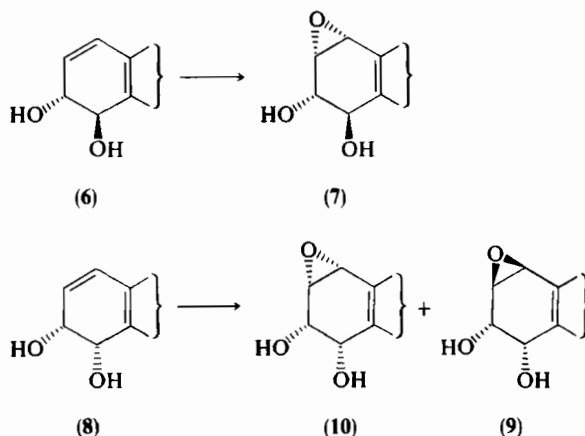
<sup>7</sup> D. R. Thakker, W. Levin, H. Yagi, M. Tada, A. H. Conney, and D. M. Jerina, in "Polynuclear Aromatic Hydrocarbons: Chemistry and Biological Effects" (A. Bjørseth and A. J. Dennis, eds.), p. 267. Battelle Press, Columbus, Ohio, 1980.

<sup>8</sup> E. Vogel and H. Gunther, *Angew. Chem., Int. Ed. Engl.* **6**, 385 (1967).

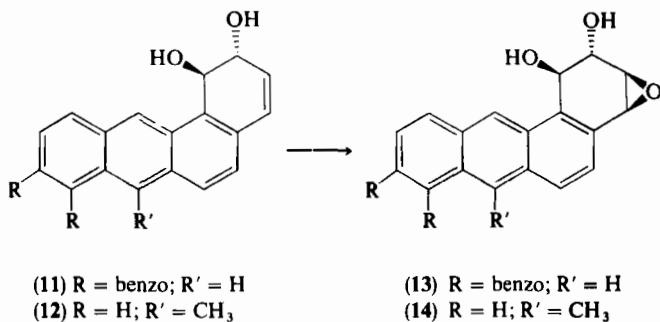
<sup>9</sup> K. Ishikawa, H. C. Charles, and G. W. Griffin, *Tetrahedron Lett.*, 427 (1977).

<sup>10</sup> H. M. Lee and R. G. Harvey, *J. Org. Chem.* **44**, 4948 (1979).





The first example of *syn* stereoselective epoxidation of arene dihydrodiols was reported in 1981.<sup>11</sup> The *trans*-dihydrodiols **11** and **12**, when treated with a 10-fold excess of MCPBA in tetrahydrofuran (THF) at room temperature, gave stereoselectively the *syn*-diol epoxides **13** and **14**, respectively. This stereoselectivity has been ascribed to the operation of steric control by the axial benzylic hydroxy group; the equatorial hydroxy group does not exert such control. The isomeric 9,10-epoxides of 7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene can be prepared by the same method.<sup>12</sup>

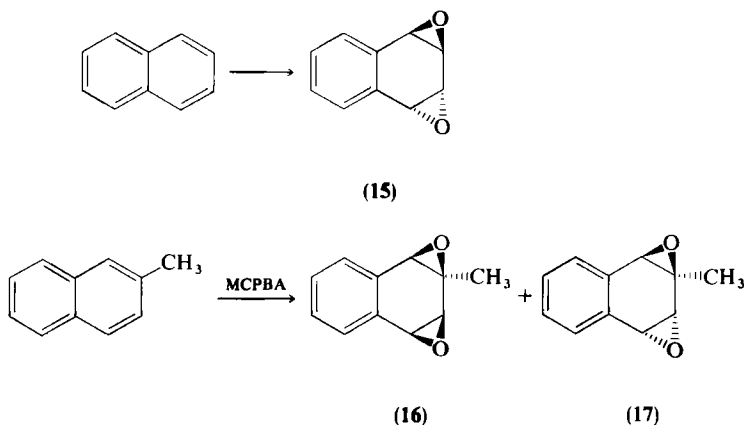


The stereoselective synthesis of *syn*- and *anti*-diepoxides has also been achieved by using MCPBA. Naphthalene with MCPBA in methylene chloride-aqueous sodium bicarbonate gave 15–20% of *anti*-1,2:3,4-naphthalene diepoxide **15**. However, 2-methylnaphthalene under similar conditions gave mixed *syn*-(**16**) and *anti*-(**17**) 1,2:3,4-naphthalene diepoxides.<sup>13</sup>

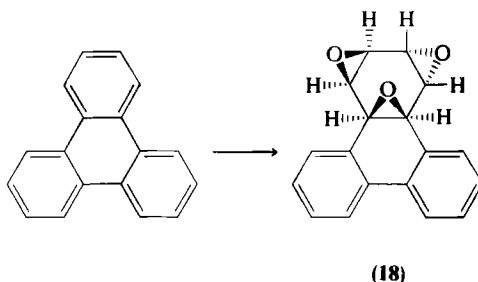
<sup>11</sup> H. M. Lee and R. G. Harvey, *Tetrahedron Lett.*, 1657 (1981).

<sup>12</sup> F. A. Beland and R. G. Harvey, *J.C.S. Chem. Commun.*, 84 (1976).

<sup>13</sup> K. Ishikawa and G. W. Griffin, *Angew Chem., Int. Ed. Engl.* **16**, 171 (1977).



The synthesis of triphenylene triepoxide (18) in 10–55% yield has been accomplished by treating triphenylene with 6–20 equivalents of MCPBA in methylene chloride–aqueous sodium bicarbonate.<sup>14</sup>



## 2. With Sodium Hypochlorite

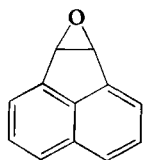
Another synthetic method involves treating the parent aromatic hydrocarbon with sodium hypochlorite in water–chloroform, using phase transfer agents like tetrabutylammonium hydrogen sulfate or benzyltrimethylammonium chloride.<sup>15</sup> The epoxides are formed in high yields. The rate is pH dependent, and epoxide formation is most facile at pH 8–9. Many K-region arene oxides like **1**,<sup>16</sup> **5**, acenaphthylene 1,2-oxide (**19**), 1-azaphenanthrene 5,6-oxide (**20**), 4-azaphenanthrene 5,6-oxide (**21**), 1,10-phenanthroline 5,6-oxide

<sup>14</sup> H. C. Charles, R. J. Baker, L. M. Trefonas, and G. W. Griffin, *J. C. Soc. Chem. Commun.*, 1075 (1980).

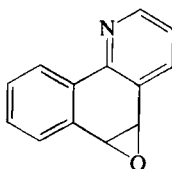
<sup>15</sup> S. Krishnan, D. G. Kuhn, and G. A. Hamilton, *J. Am. Chem. Soc.* **99**, 8121 (1977).

<sup>16</sup> Nippon Shokubai Kogaku Kogyo Co., Ltd., Tokyo Koho, Japanese Patent 81 12,335(1979) [*CA* **94**, 208611 (1981)].

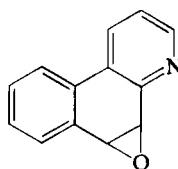
(22), 2-acetylphenanthrene 9,10-oxide (23), and 9-dodecylphenanthrene 9,10-oxide (24) have been prepared by this method. Naphthalene under these conditions gives the *syn*-diepoxide (25, 19%).<sup>16</sup>



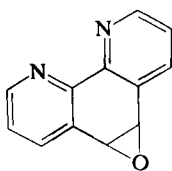
(19)



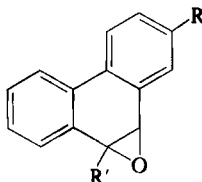
(20)



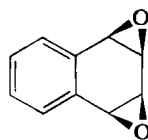
(21)



(22)



(23) R = COCH<sub>3</sub>; R' = H  
(24) R = H; R' = C<sub>12</sub>H<sub>25</sub>

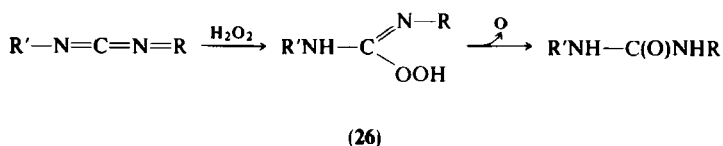


(25)

### 3. With Carbodiimides and Hydrogen Peroxide

Phenanthrene and pyrene on treatment with diisopropylcarbodiimide, hydrogen peroxide, and acetic acid in ethyl acetate at room temperature give **1** and **4** in 28% and 27% yields, respectively.<sup>17</sup> Similar reaction occurs with dicyclohexylcarbodiimide and cyclohexylbenzylcarbodiimide. The hydrogen peroxide can be either 98% or a 30% aqueous solution. Use of silica gel, Dowex 50W-X8, or diphenylphosphinic acid instead of acetic acid is also permissible. However, because of the sensitivity of arene oxides toward strong acids, hydrochloric, sulfuric, or polyphosphoric acids cannot be used.

Presumably, peroxy-carboximidic acid (**26**) is formed by the reaction of carbodiimides and hydrogen peroxide. This is eventually converted to the urea derivative during epoxidation after transfer of oxygen to the substrate.

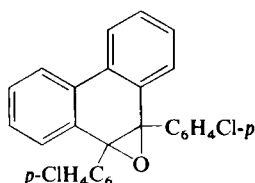


<sup>17</sup> S. Krishnan, D. G. Kuhn, and G. A. Hamilton, *Tetrahedron Lett.*, 1369 (1977).

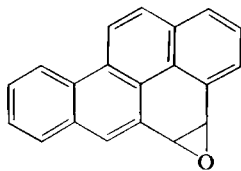
B. FROM *trans*-1,2-GLYCOLS

## 1. With Dimethylformamide–Dimethyl Acetal

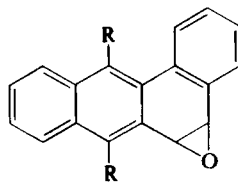
*trans*-1,2-Glycols of aromatic hydrocarbons, easily accessible by lithium aluminum hydride reduction of the corresponding 1,2-quinones, can be dehydrated with dimethylformamide–dimethyl acetal (DMF–DMA) in dry DMF–THF.<sup>18,19</sup> Advantage is taken of the fact that DMF–DMA is a nonacidic dehydrating agent and forms DMF and methanol, which are compatible with the arene oxides. Epoxides (**1**, 64%),<sup>20</sup> its 9,10-dimethyl derivative (**2**, 1.7%), and its 9,10-di(*p*-chlorophenyl) derivative (**27**, 68%),<sup>21</sup> **4**, as well as benzo[*a*]pyrene 4,5-oxide (**28**), benz[*a*]anthracene 5,6-oxide (**29**), and 7,12-dimethylbenz[*a*]anthracene 5,6-oxide (**30**) have been prepared by this method.<sup>22</sup>



(27)



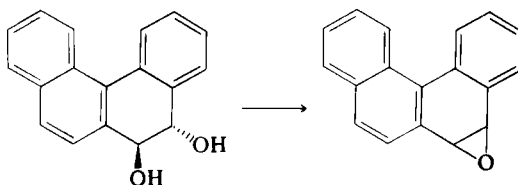
(28)



(29) R = H

(30) R = CH<sub>3</sub>2. With *p*-Toluenesulfonyl Chloride–Sodium Hydride

The cyclization of *trans*-1,2-glycols can also be brought about, using *p*-toluenesulfonyl chloride and sodium hydride. Benzo[*c*]phenanthrene 5,6-oxide (**31**) has been prepared in 8% yield from the corresponding *trans*-glycol (**32**).<sup>23</sup>



(32)

(31)

<sup>18</sup> S. H. Goh and R. G. Harvey, *J. Am. Chem. Soc.* **95**, 242 (1973).

<sup>19</sup> S. H. Goh and R. G. Harvey, *Tetrahedron Lett.*, 1491 (1974).

<sup>20</sup> C. Cortez and R. G. Harvey, *Org. Synth.* **58**, 12 (1978).

<sup>21</sup> D. Avnir, A. Grauer, D. Dinur, and J. Blum, *Tetrahedron* **31**, 2457 (1975).

<sup>22</sup> R. G. Harvey, S. H. Goh, and C. Cortez, *J. Am. Chem. Soc.* **97**, 3468 (1975).

<sup>23</sup> M. Croisey-Delcey, Y. Ittah, and D. M. Jerina, *Tetrahedron Lett.*, 2849 (1979).

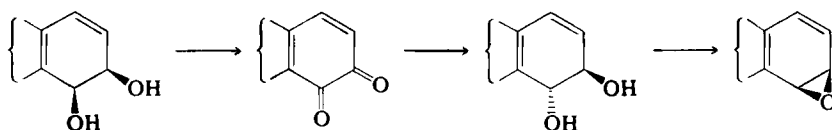
### 3. With a Sulfurane Derivative

The *trans*-dihydrodiols can also be cyclodehydrated in about 1 min to arene oxides using 3 mol of diphenyldi-(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propoxy)sulfurane,  $\text{Ph}_2\text{S}[\text{OC}(\text{CF}_3)_2\text{Ph}]$  (33) in anhydrous methylene chloride at room temperature. Thus, **1** and **4** were prepared in quantitative yields, whereas **28** and **29** were obtained in 60–65% yields.<sup>24</sup>

## C. FROM *cis*-1,2-GLYCOLS

### 1. By Conversion to *trans*-1,2-Glycols

The *cis*-1,2-glycols, obtainable from the parent aromatic hydrocarbon by osmium tetroxide hydroxylation, can be converted to the corresponding *trans*-1,2-glycols by oxidation–reduction, using a mixture of dimethyl sulfoxide, sulfur trioxide, and pyridine, followed by lithium aluminum hydride reduction. The *trans*-1,2-glycols can be dehydrated to arene oxides using DMF–DMA as mentioned above. Benzo[*a*]pyrene 4,5-oxide (**28**) and 7,12-dimethylbenz[*a*]anthracene 5,6-oxide (**30**) have been prepared by this method in 68 and 80% yields, respectively.<sup>18</sup>



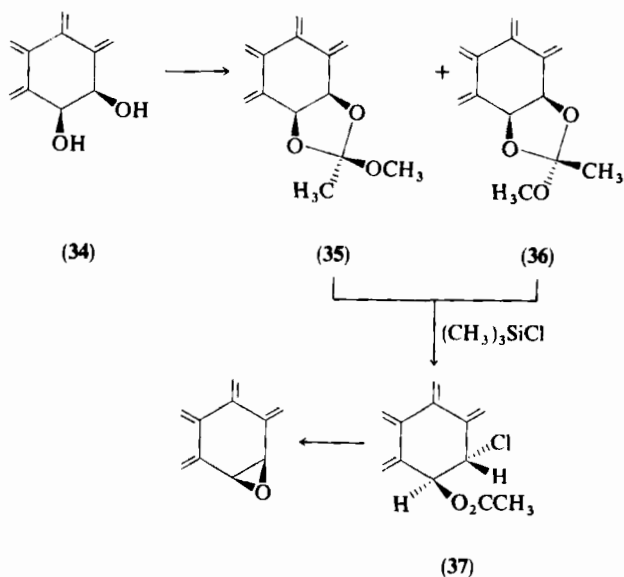
### 2. With Orthoesters

Dansette and Jerina<sup>25</sup> found that *cis*-1,2-glycols (**34**) on treatment with trimethyl orthoacetate in refluxing benzene containing a trace of benzoic acid are converted to an enantiomeric mixture of 2-methyl-2-methoxydioxolanes (orthoesters) (**35** and **36**). On reaction of this mixture with trimethylsilyl chloride, substitution with inversion takes place, and *trans*-chlorohydrin acetate (**37**) is formed. The chlorohydrin acetate is cyclized to an arene oxide on treatment with sodium methoxide.

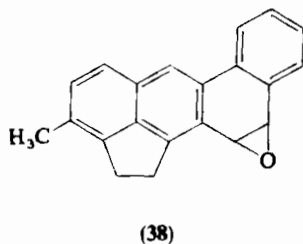
Phenanthrene 9,10-oxide (**1**, 52%), benz[*a*]anthracene 5,6-oxide (**29**, 43%), 7,12-dimethylbenz[*a*]anthracene 5,6-oxide (**30**, 52%), 3-methylcholanthrene

<sup>24</sup> T. Okamoto, K. Shudo, N. Miyata, Y. Kitahara, and S. Nagata, *Chem. Pharm. Bull.* **26**, 2014 (1978).

<sup>25</sup> P. Dansette and D. M. Jerina, *J. Am. Chem. Soc.* **96**, 1224 (1974).



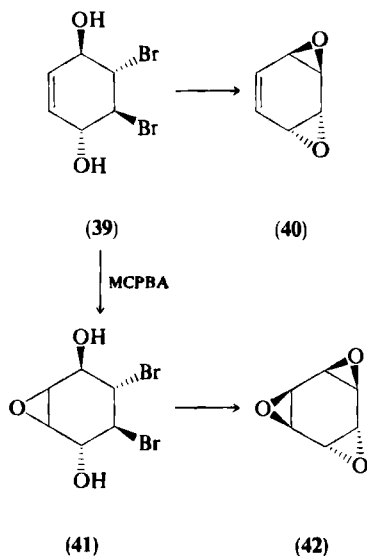
11,12-oxide (38, 45%), pyrene 4,5-oxide (4, 45%), and benzo[*a*]pyrene 4,5-oxide (28, 56%), have been so prepared.<sup>25</sup>



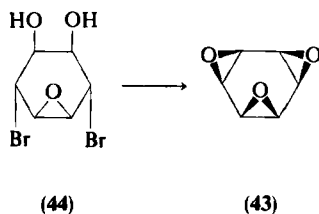
## D. FROM BROMOHYDRINS

### 1. By Treatment with a Base

*trans*-Bromohydrins can be converted to the corresponding arene oxides on treatment with bases like potassium *t*-butoxide, potassium hydroxide, monosodium glycolate, diazobicyclononane (DBN), and sodium methoxide in moderate yields. Even the diepoxides and triepoxides have been prepared by this method. Thus *anti*-benzene diepoxide (40) and *anti*-benzene triepoxide (42) have been prepared by treatment of corresponding bromohydrins 39 and



**41** with potassium hydroxide<sup>26</sup> in 38 and 45% yields, respectively. The *syn*-benzene triepoxide (**43**) is similarly obtained (35–40%) by the action of potassium hydroxide on bromohydrin **44**.<sup>27</sup>



Similarly, epoxides of benz[*a*]anthracene and benzo[*a*]pyrene have been prepared by treatment of the corresponding bromohydrins with potassium *t*-butoxide.

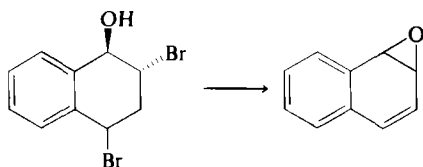
Naphthalene 1,2-oxide (**45**) can be prepared by treatment of bromohydrin **46** with sodium methoxide in THF. Cyclization and dehydrobromination are achieved in a single pot.<sup>28</sup> By this method, the non-*K*-region epoxide phenanthrene 1,2-oxide (**47**) and the bay-region oxide phenanthrene 3,4-oxide (**48**) have also been prepared.<sup>28</sup> The syntheses of homobenzene analog **49** and

<sup>26</sup> H. J. Altenbach, H. Stegelmeier, and E. Vogel, *Tetrahedron Lett.*, 3333 (1978).

<sup>27</sup> E. Vogel, H. J. Altenbach, and C. D. Sommerfeld, *Angew. Chem., Int. Ed. Engl.* **11**, 939 (1972).

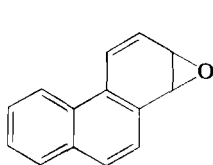
<sup>28</sup> H. Yagi and D. M. Jerina, *J. Am. Chem. Soc.* **95**, 243 (1973).

compound **50** have been reported using DBN as well as potassium *t*-butoxide.<sup>29</sup>

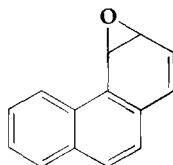


(46)

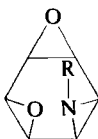
(45)



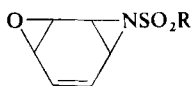
(47)



(48)



(49)



(50)

## 2. From Bromohydrin Acetates

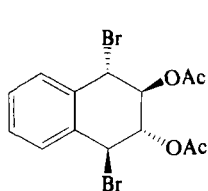
Analogous to the reaction of bromohydrins, the reaction of bromohydrin acetates with bases like potassium hydroxide in methanol or sodium methoxide in THF gives epoxides. The bromohydrin acetate (**51**) of naphthalene<sup>30</sup> on treatment with potassium hydroxide gives the *anti*-naphthalene diepoxide **15**, whereas the bromohydrin trifluoroacetate derivative of phenanthrene (**52**) with sodium methoxide gives phenanthrene 1,2-oxide (**47**).<sup>31</sup> The latter is a general method for the synthesis of non-K-region arene oxides. Using this method, **48**, **45**, benzo[*a*]pyrene 7,8- and 9,10-oxides (**53** and **54**), respectively, have been prepared in more than 90% yields.

<sup>29</sup> H. Prinzbach, K. H. Mueller, C. Kaiser, and D. Hunkler, *Tetrahedron Lett.*, 3475 (1980).

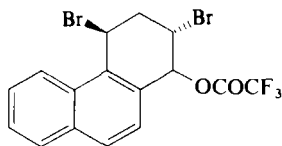
<sup>30</sup> E. Vogel, H. H. Klug, and M. Schäfer-Ridder, *Angew. Chem. Int. Ed. Engl.* **15**, 229 (1976).

<sup>31</sup> H. Yagi and D. M. Jerina, *J. Am. Chem. Soc.* **97**, 3185 (1975).

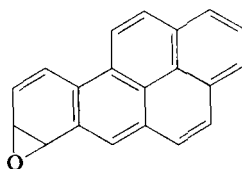




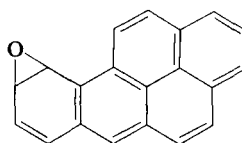
(51)



(52)

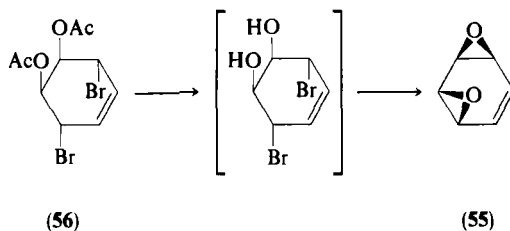


(53)



(54)

Similarly, syn-benzene diepoxide (55) can be prepared by the action of potassium hydroxide on bromohydrin acetate 56.<sup>32</sup>

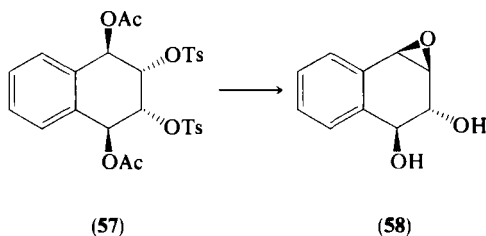


(56)

(55)

### 3. From Arene Tetrahydrotetrol Esters

The tetrahydrotetraol triester 57, on stirring with sodium carbonate in methanol, produces 90% of the ( $\pm$ )-diol epoxide 58.<sup>33</sup> The dimesylate



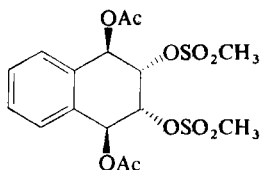
(57)

(58)

<sup>32</sup> H. J. Altenbach and E. Vogel, *Angew. Chem., Int. Ed. Engl.* **11**, 937 (1972).

<sup>33</sup> R. R. Schmidt and R. Angerbauer, *Angew. Chem., Int. Ed. Engl.* **18**, 304 (1979).

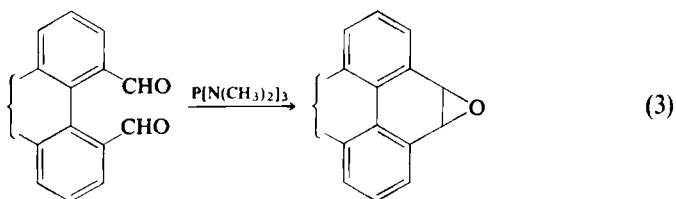
derivative **59** is instead converted to *syn*-naphthalene dioxide **25** in 82% yield. Inasmuch as **25** cannot be obtained in high yield<sup>14</sup> by direct epoxidation of naphthalene, this is an important method of preparation.<sup>33</sup>



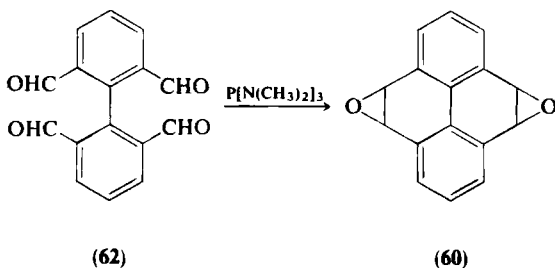
(59)

### E. FROM SECO DERIVATIVES

The first arene oxides to be synthesized (1964) were obtained by the cyclization of appropriate seco derivatives. *o,o*-Diformylbiphenyl derivatives, when treated with Mark's reagent [tris(dimethylamino)phosphine], gave arene oxides [Eq. (3)]. Thus K-region epoxides from phenanthrene and its analogs, benz[*a*]anthracene and its 7,12-dimethyl analog, have been prepared.<sup>34</sup>

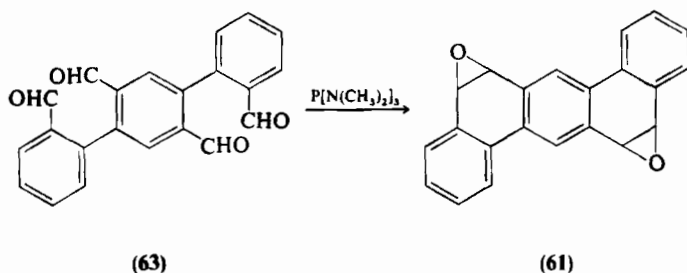


The diepoxides **60** and **61** of pyrene and dibenz[*a,h*]anthracene have been prepared in 19 and 80% yields<sup>35</sup> from **62** and **63**, respectively. And

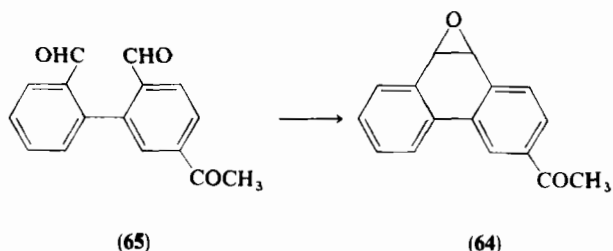


<sup>34</sup> M. S. Newman and S. Blum, *J. Am. Chem. Soc.* **86**, 5598 (1964).

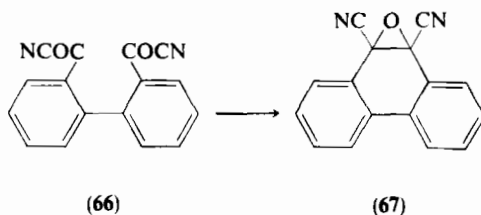
<sup>35</sup> S.C. Agarwal and B. L. Van Duuren, *J. Org. Chem.* **40**, 2307 (1975).



3-acetylphenanthrene 9,10-oxide (64) was prepared from the secodialdehyde derivative 65 using Mark's Reagent.<sup>36</sup> The dicyanocarbonyl derivative 66 has



also been cyclized to the bridgehead dicyano-substituted phenanthrene oxide 67 using triethyl phosphite.<sup>36</sup>



## F. MISCELLANEOUS METHODS

### 1. Electrochemical Oxidation

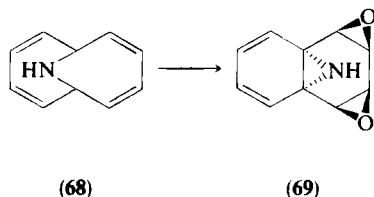
A mixture of arene oxides and quinones is reported to have been formed by the electrochemical oxidation of aromatic hydrocarbons in an atmosphere of oxygen or oxygen-containing gaseous mixtures. The method is patented and details have not been disclosed.<sup>37</sup>

<sup>36</sup> G. W. Griffin, S. K. Satra, N. E. Brightwell, K. Ishikawa, and N. S. Bhacca, *Tetrahedron Lett.*, 1239 (1976).

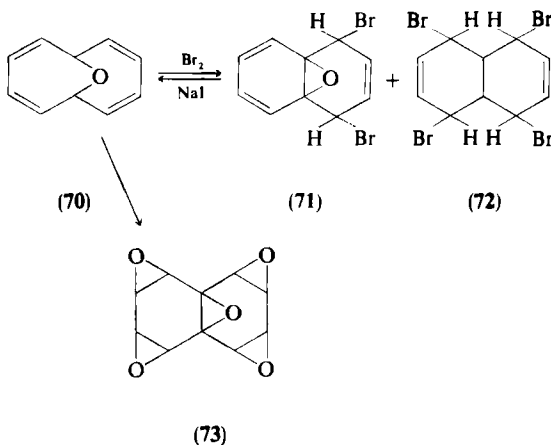
<sup>37</sup> M. Horn, German Patent 2,721,141(1977) [*CA* 90, 54729 (1979)].

## 2. From Annulenes

When 1,6-imino-10-annulene (**68**) is oxidized with singlet oxygen and the product is thermolyzed, the homobenzene derivative **69** is formed. This, on treatment with nitrosyl chloride in the presence of triethylamine gives **25** in 5% yield.<sup>38</sup> Also, annulene **70** on treatment with bromine gives the dibromoarene



oxide **71** along with another product **72**.<sup>39</sup> Alternatively, annulene **70**, on exhaustive oxidation with singlet oxygen, produces naphthalene pentaepoxide **73**.<sup>30</sup>



## 3. From Arene Photooxides

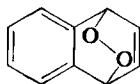
The photooxide of naphthalene (**74**) on treatment with triphenylphosphine is converted to naphthalene 1,2-oxide (**45**).<sup>40</sup> The photooxide of anthracene (**75**) is converted to *syn*-anthracene[4a,10:9,9a]diepoxide (**76**) in 78% yield by means of an interesting photochemical rearrangement.<sup>41</sup> The endoperoxide of

<sup>38</sup> E. Vogel, H. H. Klug, and M. Schaefer-Ridder, *Angew. Chem.* **88**, 268 (1976).

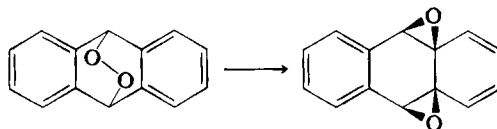
<sup>39</sup> E. Vogel, W. A. Boll, and M. Biskup, *Tetrahedron Lett.*, 1569 (1966).

<sup>40</sup> M. Schaefer-Ridder, U. Brocker, and E. Vogel, *Angew. Chem., Int. Ed. Engl.* **15**, 228 (1976).

<sup>41</sup> J. Rigandy, A. Defoin, and J. Baranne-Lafont, *Angew. Chem., Int. Ed. Engl.* **18**, 413 (1979).



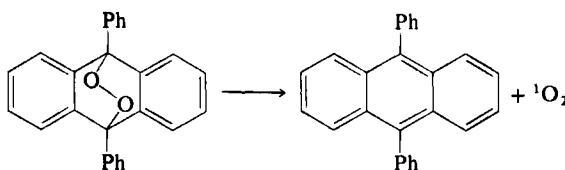
(74)



(75)

(76)

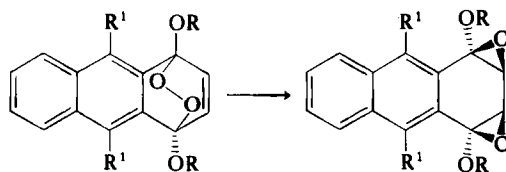
9,10-diphenylanthracene (77) in refluxing benzene liberates singlet oxygen almost quantitatively and is converted to the parent hydrocarbon (78).



(77)

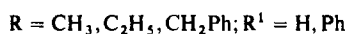
(78)

In contrast, peroxides with bridgehead alkoxy groups, such as 79 and 80, undergo the diepoxide photochemical rearrangement to diepoxides 81 and 82, respectively.<sup>42-44</sup> The resorcinol derivative 83 on reaction with singlet oxygen



(79)

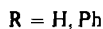
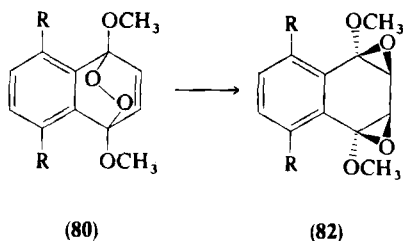
(81)



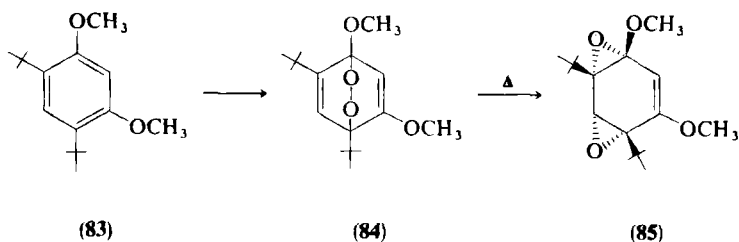
<sup>42</sup> J. Rigandy, N. C. Cohen, and N. K. Cuong, *C.R. Hebd. Seances Acad. Sci.* **264**, 1851 (1967).

<sup>43</sup> J. Rigandy, C. Deletang, D. Sparfel, and N. K. Cuong, *C.R. Hebd. Seances Acad. Sci.* **267**, 1714 (1968).

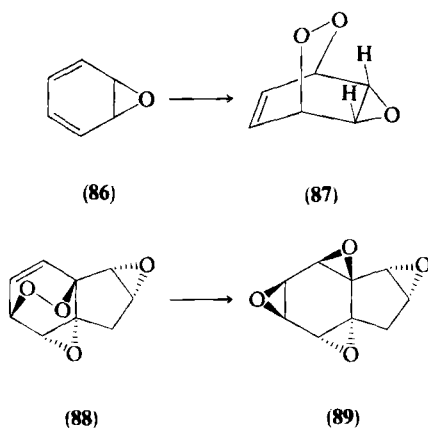
<sup>44</sup> J. Rigandy, C. Deletang, and J. J. Basselier, *C.R. Hebd. Seances Acad. Sci.* **268**, 344 (1969).



affords the peroxide **84**, which also undergoes rearrangement<sup>45</sup> to furnish the diepoxide **85**.



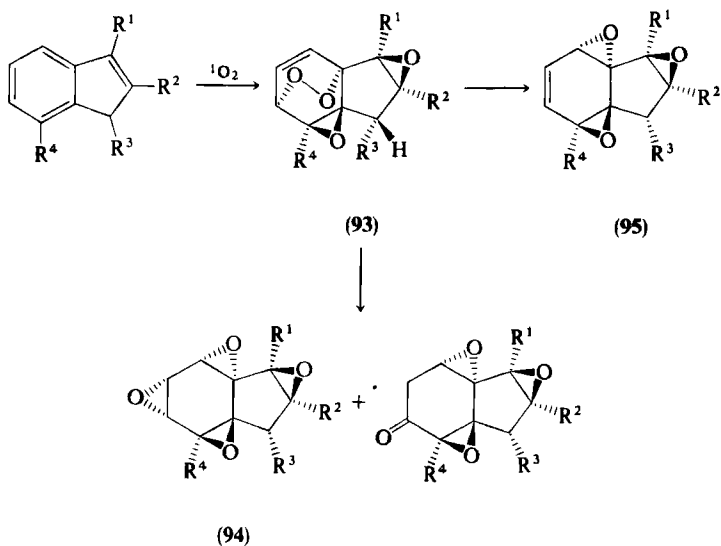
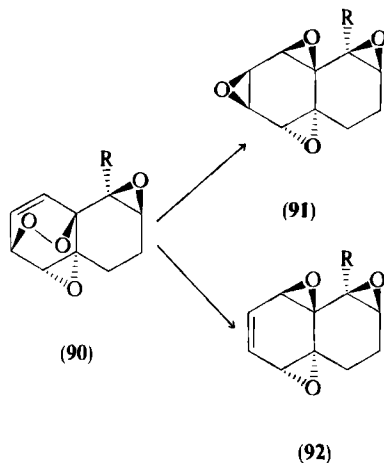
Benzene oxide (**86**), on reaction with singlet oxygen generated either from hypochlorite–hydrogen peroxide or ozone–triphenyl phosphite, forms peroxide **87** in 37% yield. This peroxide on heating in chloroform is quantitatively isomerized to *anti*-benzene trioxide (**42**).<sup>46</sup> The endoperoxide **88** is similarly



<sup>45</sup> I. Saito, S. Kato, and T. Matsuura, *Tetrahedron Lett.*, 239 (1970).

<sup>46</sup> C. H. Foster and G. A. Berchtold, *J. Am. Chem. Soc.* **94**, 7939 (1972).

converted to the tetraepoxide **89** on heating.<sup>47</sup> The analogous endoperoxidebisepoxide (**90**), obtainable from 1,2-dihydronaphthalene by reaction with singlet oxygen at  $-78^{\circ}\text{C}$  in acetone, rearranges on heating to the tetraepoxide **91**. However, on treatment with trimethyl phosphite, **90** is converted to the triepoxide **92**.<sup>48</sup>



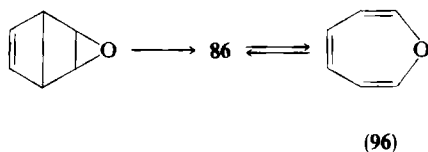
<sup>47</sup> C. S. Foote, S. Mazur, P. A. Burns, and D. Lerdal, *J. Am. Chem. Soc.* **95**, 586 (1973).

<sup>48</sup> P. A. Burns and C. S. Foote, *J. Org. Chem.* **41**, 908 (1976).

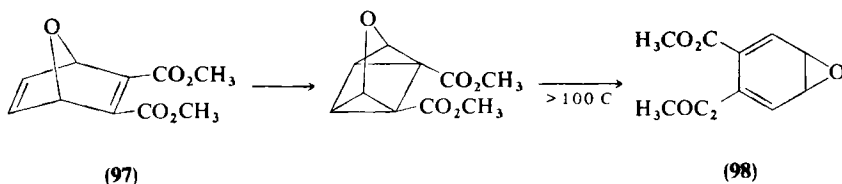
Similarly, indenenes undergo dye-sensitized photooxygenation at  $-78^{\circ}\text{C}$  in acetone to yield the usual oxygenated products, namely 2,3,7,9-diepoxy-6,9-peroxy- $\Delta^{4,5}$ -hexahydroindenenes (**93**). These compounds also undergo thermal rearrangement to form indene tetraepoxides (benzene oxides) (**94**) and are converted to 2,3,4,9:7,8-triepoxy- $\Delta^{5,6}$ -hexahydroindenenes (**95**) on treatment with trimethyl phosphite.<sup>49</sup>

#### 4. From Oxygen Heterocycles

Thermolysis or photolysis of the epoxidized Dewar benzene produces benzene oxide-oxepin (**86**  $\rightleftharpoons$  **96**) along with substantial amounts of phenol.<sup>50,51</sup> Also, photolysis followed by thermolysis of the 1:1 Diels-Alder



adduct **97** from furan and dimethyl acetylenedicarboxylate is reported to furnish 4,5-di(methoxycarbonyl)benzene oxide (**98**).<sup>52</sup>



#### 5. By Dehydrohalogenation Sequences

Another common method for the preparation of benzene and naphthalene epoxides is by introduction of double bonds into the dihydro precursors. This is generally achieved by bromination-dehydrobromination. Thus unsubstituted benzene oxide-oxepin (**86**  $\rightleftharpoons$  **96**) can be obtained by dehydrohalogenation of the dibromocyclohexane epoxide **99**, using a basic amine or sodium methoxide in ether.<sup>53</sup>

<sup>49</sup> P. A. Burns, C. S. Foote, and S. Mazur, *J. Org. Chem.* **41**, 899 (1976).

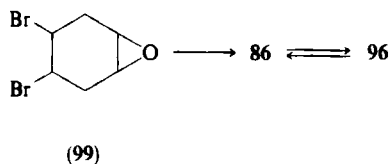
<sup>50</sup> E. E. Van Tamelen and D. Carty, *J. Am. Chem. Soc.* **89**, 3922 (1967).

<sup>51</sup> E. Boyland and P. Sims, *Biochem. J.* **90**, 391 (1964).

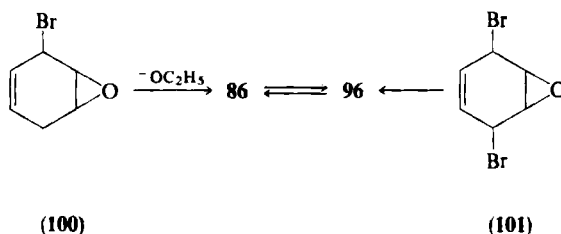
<sup>52</sup> H. Prinzbach, M. Argueller, and E. Druckrey, *Angew. Chem., Int. Ed. Engl.* **5**, 1039 (1966).

<sup>53</sup> E. Vogel, W. A. Boll, and H. Gunther, *Tetrahedron Lett.*, 609 (1965).

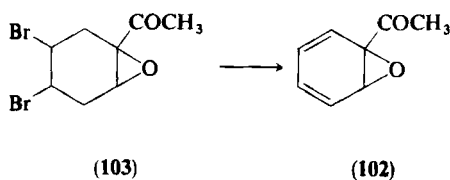




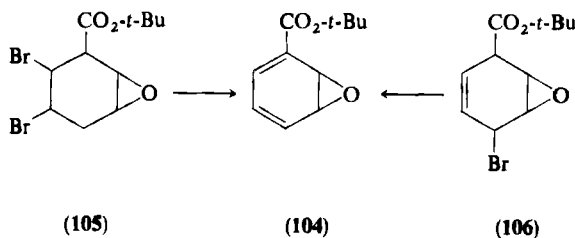
Alternatively, action of alkoxide base on the unsaturated monobromo epoxide **100** or action of sodium iodide on the unsaturated dibromo epoxide **101** also produces  $86 \rightleftharpoons 96$ .<sup>54</sup> Methyl and other substituted benzene oxides have been prepared in a similar way from the bromo precursors.<sup>8</sup>



Dehydrohalogenation has also been utilized in the synthesis of 1-acetylbenzene oxide (**102**) from the dibromo compound **103**.<sup>8</sup>

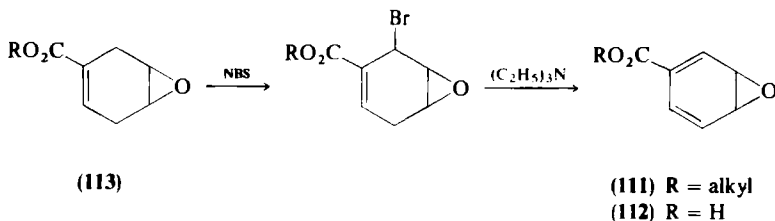
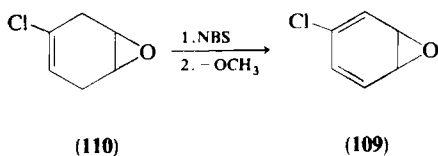
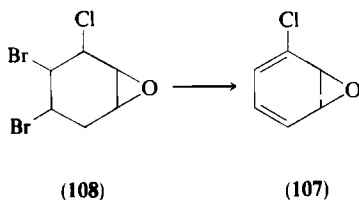


The 3-*t*-butoxycarbonylbenzene oxide **104** has been prepared by dehydrobromination of either the saturated dibromo epoxide **105** or the unsaturated monobromo epoxide **106**.<sup>55</sup> Similarly, 3-chlorobenzene oxide (**107**) is prepared by dehydrobromination of the dibromochloro epoxide **108**,<sup>55</sup> and 4-



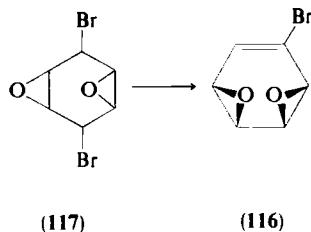
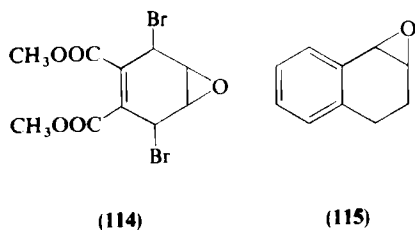
<sup>54</sup> R. Schubart, Ph.D. Thesis, University of Kohn (1967).

<sup>55</sup> B. A. Chaiasson and G. A. Berchtold, *J. Org. Chem.* **42**, 2008 (1977). H. G. Selander, D. M. Jerina, D. E. Piccolo, E. Daniel, and G. Berchtold, *J. Am. Chem. Soc.* **97**, 4428 (1975).



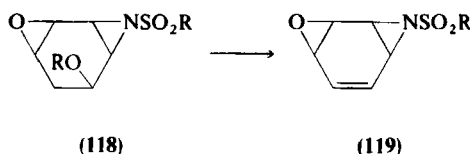
chlorobenzene oxide (109) by bromination-dehydrobromination of 110.<sup>55</sup> 4-Alkoxycarbonylbenzene oxides (111) and the corresponding free acid (112) have also been synthesized by bromination-dehydrobromination of 113.<sup>56</sup>

Elimination has also been brought about by potassium iodide: e.g., dibromoepoxide 114 gives 98.<sup>8</sup>

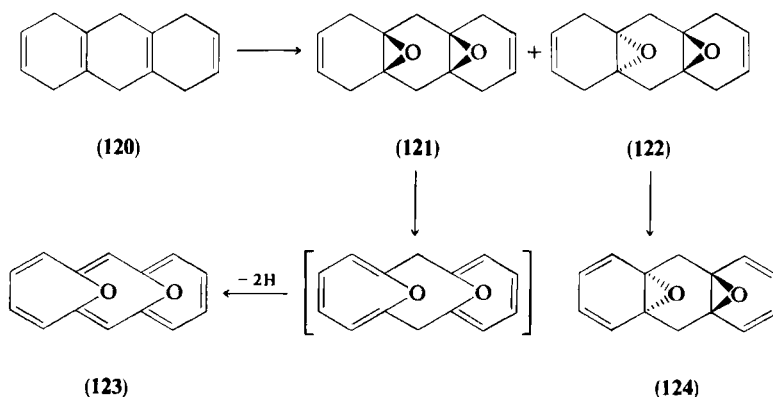


<sup>56</sup> R. M. DeMarinis and G. A. Berchtold, *J.C.S. Chem. Commun.*, 810 (1971).

Naphthalene 1,2-oxide (**45**) has been obtained by bromination (NBS)-dehydrobromination (DBN) of tetralin 1,2-epoxide (**115**).<sup>57</sup> Sodium in liquid ammonia gives diepoxide **116** from **117**.<sup>58</sup> Also, the saturated compound **118** with potassium *t*-butoxide in THF yields the oxazabis-6-homobenzene system (**119**, 80%).<sup>29</sup>



Hexahydroanthracene (**120**) on treatment with perbenzoic acid produces the isomeric diepoxides **121** and **122**. The *syn*-diepoxide **121** with bromine, followed by potassium *t*-butoxide treatment, produces the annulene **123**, whereas similar reactions with the *anti*-diepoxide **122** give the arene oxide **124**.<sup>8</sup>



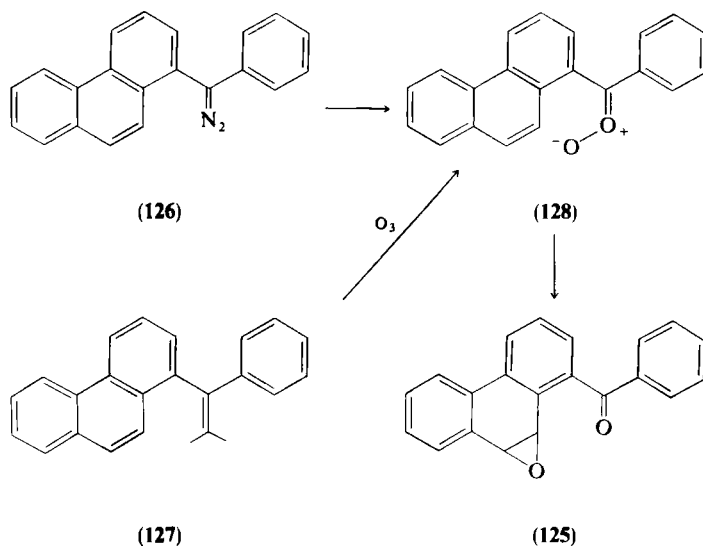
## 6. By Intramolecular Oxygen Trapping

Murray and Benavali<sup>59</sup> have recently reported the preparation of 1-benzoylphenanthrene 9,10-oxide (**125**) by photolysis in the presence of oxygen of 1-phenanthrylphenyldiazomethane (**126**) and also by ozonolysis of 1-(1-phenanthryl)-1-phenyl-2-methylpropene (**127**) in 7 and 4% yield, respectively. The carbonyl oxide **128**, formed in both cases, reacts intramolecularly to give **125**.

<sup>57</sup> E. Vogel and F. G. Klaerner, *Angew. Chem., Int. Ed. Engl.* **7**, 374 (1968).

<sup>58</sup> E. Vogel, H. J. Attenbach, and D. Cremer, *Angew. Chem., Int. Ed. Engl.* **11**, 935 (1972).

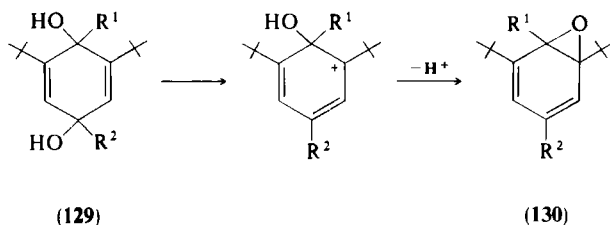
<sup>59</sup> R. M. Murray and R. Banavali, *Tetrahedron Lett.*, 2327 (1983).



The reaction does not have preparative significance. However, it has been surmised that polycyclic aromatic hydrocarbons adsorbed on atmospheric particulate matter can become activated as a result of atmospheric oxidation. Samples of such materials could display a degree of mutagenicity not associated with inactivated hydrocarbons. Although in many cases the precise nature of the oxidant is not clear, Pitts *et al.*<sup>60</sup> have been able to show that ozone can convert benzo[*a*]pyrene, adsorbed on a glass filter, to its 4,5-oxide (28).

### 7. From 1,4-Dihydro-1,4-dihydroxybenzenes

The acid-catalyzed dehydration of substituted 1,4-dihydro-1,4-dihydroxybenzenes (129) forms the corresponding arene oxides (130) in poor yield along with several other products.<sup>61</sup>

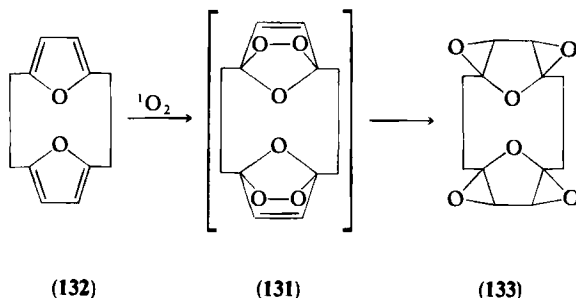


<sup>60</sup> J. N. Pitts, D. M. Lokensgard, P. S. Ripley, K. A. Van Cauwenberghe, L. Van Vaeck, S. D. Shaffer, A. J. Thill, and W. L. Belser, Jr., *Science* **210**, 1347 (1980).

<sup>61</sup> S. Berger, G. Henes, and A. Rieker, *Tetrahedron Lett.*, 1257 (1971).

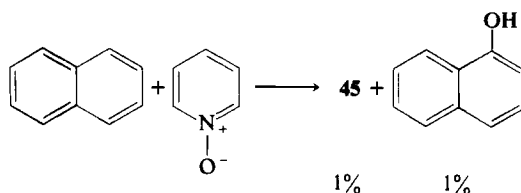
### 8. From Ozonides

The diazonide **131** obtainable from furanophene (**132**) with singlet oxygen is isomerized to the tetraepoxide **133** when photolyzed in methylene chloride.<sup>62</sup>



### 9. Using Pyridine N-Oxide

The first example of direct epoxidation of an aromatic double bond was reported by Jerina *et al.*<sup>63</sup> The reaction involves photolysis of aromatic *N*-oxides to give **45** in 1% yield. The method does not have preparative significance.



### 10. By $\gamma$ Radiolysis

Radiolysis of liquid carbon dioxide with phenanthrene gives its 9,10-oxide (**1**), although in poor yield, along with other products.<sup>64</sup>

## G. SYNTHESIS OF OPTICALLY ACTIVE ARENE OXIDES

Akhtar and Boyd<sup>65</sup> found that the diastereomers of *trans*-2-bromo-1-menthoxyacetoxy-1,2,3,4-tetrahydronaphthalene (**134**), prepared by the re-

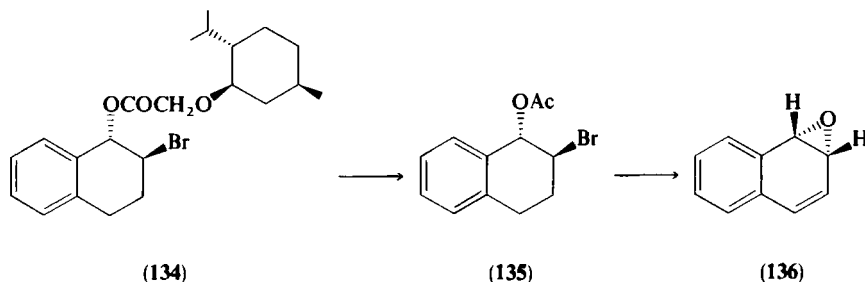
<sup>62</sup> H. H. Wasserman and R. Kitzing, *Tetrahedron Lett.*, 5315 (1969).

<sup>63</sup> D. M. Jerina, D. R. Boyd, and J. W. Daly, *Tetrahedron Lett.*, 457 (1970).

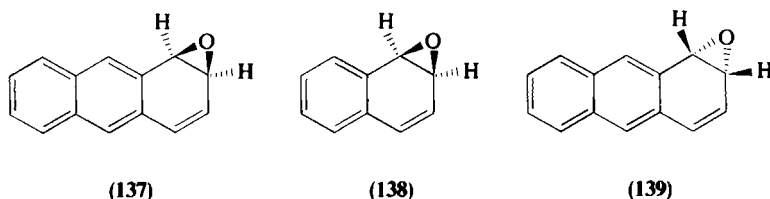
<sup>64</sup> S. Goto, A. Hori, S. Takamuku, and H. Sakurai, *Bull. Chem. Soc. Jpn.* **51**, 1569 (1978).

<sup>65</sup> M. N. Akhtar and D. R. Boyd, *J.C.S. Chem. Commun.*, 916 (1975).

action of the 1-hydroxy analog and (–)-menthoxyacetyl chloride in the presence of pyridine, could be separated by chromatography. Compound (1*S*,2*S*)-(134), on sequential treatment with diborane and acetic anhydride, furnishes the acetoxy analog 135, which with NBS, followed by sodium methoxide treatment, produced the (1*S*,2*R*)-epoxide of naphthalene (136).<sup>65</sup> The anthracene analog could be prepared in a similar manner.



Naphthalene 1,2-oxide (136), a non-K-region epoxide, shows low thermal stability. Anthracene 1,2-oxide, on the other hand, is stable at ambient temperatures for several weeks. Preparation of (+)-(1*R*,2*S*)-anthracene 1,2-oxide (137), using the above method, constitutes the first example of preparation of an optically pure arene oxide. However, the non-K-region oxides of phenanthrene, namely, its 1,2- and 3,4-oxides (47 and 48), obtained from chiral precursors, racemize fast.<sup>66</sup> Perturbational molecular orbital calculations indicate that epoxide–oxepin valence tautomerism is possible. However, the oxepin could not be detected by NMR.



The (+)-1,2-epoxides of naphthalene (138) and anthracene (137) can be prepared using a similar sequence from the corresponding (–)-menthoxyacetyl derivatives of *trans*-2-bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalene and anthracene, whereas the (–)-epoxides (136 and 139) are obtainable from the (+)-menthoxyacetyl derivatives.<sup>67</sup> The configurations of these compounds are determined by NMR analyses and correlation with alcohols of known configuration. Solid oxide 138 is unstable, whereas

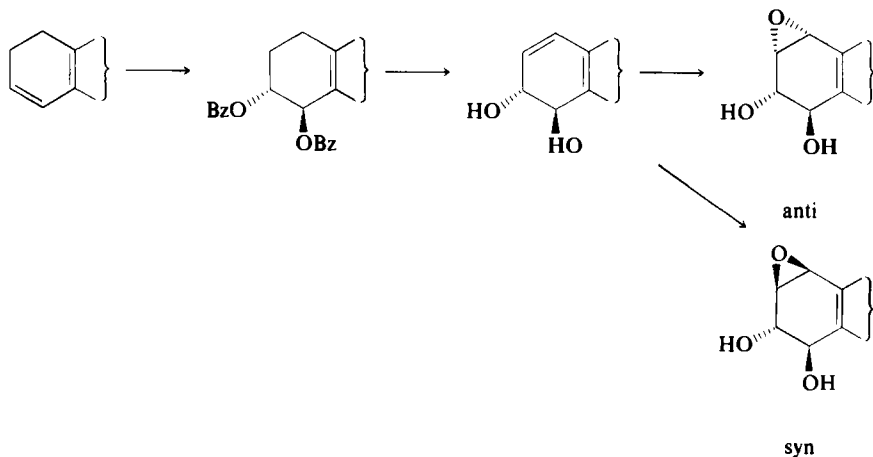
<sup>66</sup> D. R. Boyd, J. D. Neill, and M. E. Stubbs, *J.C.S. Chem. Commun.*, 873 (1977).

<sup>67</sup> M. N. Akhtar, D. R. Boyd, and J. G. Hamilton, *J.C.S. Perkin I*, 2437 (1979).

compound **137** is relatively stable in its crystalline form and remains unchanged for several days at room temperature. Also, oxides **137** and **138** do not appear to racemize in chloroform at room temperature over 24 h. Thus the barrier to thermal racemization of chiral arene oxides is sensitive to structural variations.

Both *trans*-3,4-dihydroxy-3,4-dihydrobenz[*a*]anthracene and *trans*-1,2-dihydroxy-1,2-dihydrochrysene are known proximate carcinogenic agents derived from the respective hydrocarbons. Yagi *et al.*<sup>68</sup> have resolved the tetrahydro analogs of these dihydrodiols by chromatographic separation of their diastereomeric bisesters with (–)-menthoxy acetic acid and converted the resultant tetrahydrodiols to the corresponding optically pure dihydrodiols. Thus the (+)-tetrahydrodiols lead to the (–)-dihydrodiols both with *R,R* configuration. Assignment of configuration in the chrysene series has been achieved through the application of the exciton chirality circular dichroism technique to the bis(*p*-dimethylaminobenzoate) of (–)-*trans*-1,2-dihydroxy-1,2,3,4-tetrahydrochrysene. The synthesis of + and – enantiomers as well as of the diastereomeric pair of bay-region diol epoxides has been achieved by epoxidizing the double bond of the dihydro diols either *syn* or *anti* to the benzylic hydroxy group.

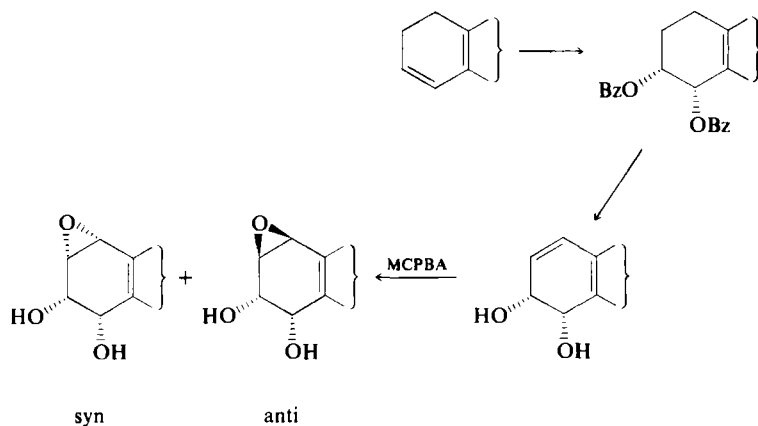
The *syn*- and *anti*-diol epoxides of benz[*a*]anthracene and benzo[*a*]pyrene have been prepared from dihydroarenes by sequential Prevost reaction with silver benzoate–iodine, dehydrogenation, methanolysis, and epoxidation, e.g.,



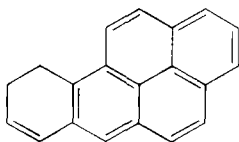
Whereas the *trans*-diols on epoxidation with MCPBA give *anti*-diol epoxides, the *cis*-diols give a 1:1 mixture of *anti*- and *syn*-diol epoxides.<sup>69</sup> Thus

<sup>68</sup> H. Yagi, K. P. Vyas, M. Tada, D. R. Thakker, and D. M. Jerina, *J. Org. Chem.* **47**, 1110 (1982).

<sup>69</sup> P. P. Fu and R. G. Harvey, *Tetrahedron Lett.*, 2059 (1977).



the dihydrobenzo[*a*]pyrene (**140**) on treatment as above furnishes the *syn*- or the *anti*-diol epoxides. Dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gives higher yields (80–93%) of dioldibenzoate than does NBS–DBN (0–68%) in the above sequence.



(140)

Phenanthrene 3,4-oxide (**48**), an initial mammalian metabolite of phenanthrene, when prepared from optically pure precursors, is optically active but racemizes very fast at ambient temperature.<sup>70</sup>

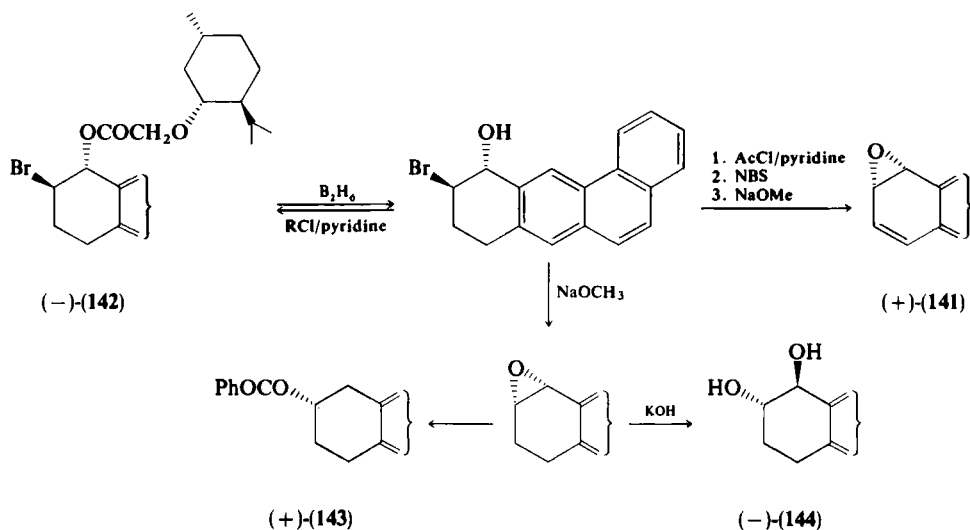
(+)-Benz[*a*]anthracene 10,11-oxide (**141**) has been obtained in optically pure form by a four-step synthesis from (–)-*trans*(10*R*, 11*R*)-10-bromo-11-(menthoxyacetoxy)-8,9,10,11-tetrahydrobenz[*a*]anthracene (**142**), which is separated from its diastereomers by recrystallization. The configuration of (+)-(**141**) was established as 10*S*, 11*R* by application of the exciton chirality method to the CD curve of the benzoate (+)-(**143**) and by correlation of stereochemistry between (+)-(**143**), (–)-(**144**), and (+)-(**141**).<sup>71</sup>

(+)-Benz[*a*]anthracene 5,6-oxide (**145**) has been synthesized in 30% optical

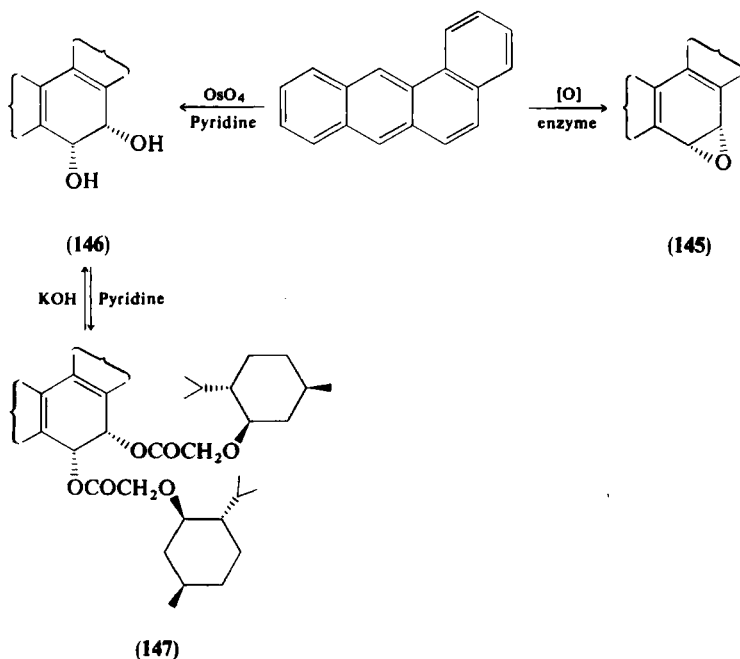
<sup>70</sup> D. R. Boyd, R. M. E. Greene, J. D. Neill, M. E. Stubbs, H. Yagi, and D. M. Jerina, *J. C. S. Perkin I*, 1477 (1981).

<sup>71</sup> D. R. Boyd, G. S. Gadaginamath, N. D. Sharma, A. F. Drake, S. F. Mason, and D. M. Jerina, *J.C.S. Perkin I*, 2233 (1981).



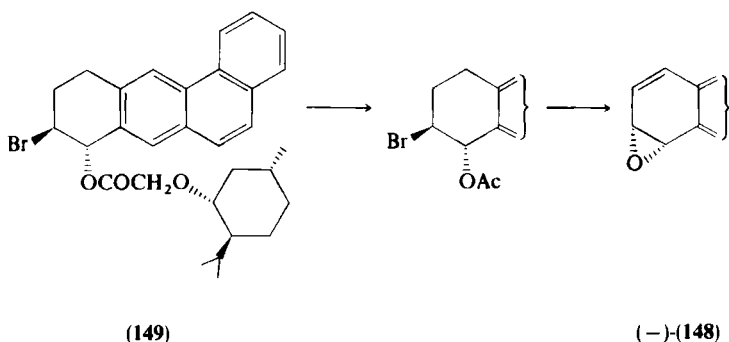


yield, using partially resolved (+)-*cis*-5,6-dihydroxy-5,6-dihydrobenz[*a*]-anthracene (146), obtainable by chromatographic resolution of the (-)-*cis*-5,6-dimethoxyacetoxy-5,6-dihydrobenz[*a*]anthracene diastereomers (147).<sup>71</sup>



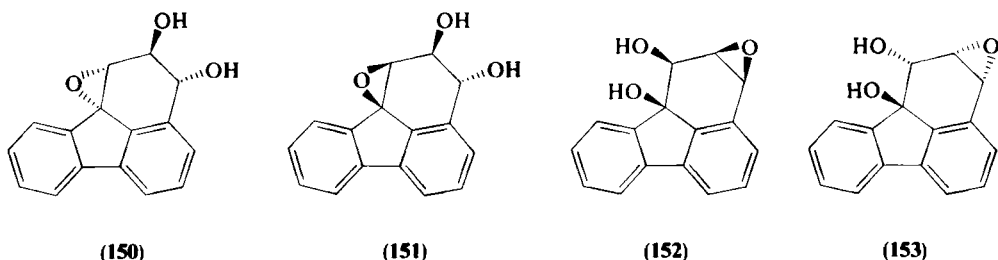
Both the oxides **141** and **145** show configurational stability at ambient temperature in accord with molecular orbital calculations.

As with **141**, the (+)- and (–)-benz[*a*]anthracene 8,9-oxides are prepared by the same sequence in optically pure form. The configuration of (–)-benz[*a*]anthracene 8,9-oxide (**148**) is unequivocally assigned as 8*S*,9*R* by configurational correlation with the tetrahydrobenz[*a*]anthracene **149**, whose absolute configuration is determined by X-ray crystallography.<sup>72</sup>



The major isolated mammalian liver metabolite of benz[*a*]anthracene, the (–)-8,9-dihydroxy-8,9-dihydroderivative, has an 8*R*,9*R* configuration and is enzymatically derived from (+)-(8*R*,9*S*)-benz[*a*]anthracene 8,9-oxide. It may be converted to *trans*-(8*R*,9*S*)-dihydroxy-(10*S*,11*R*)-epoxy-8,9,10,11-tetrahydrobenz[*a*]anthracene prior to being covalently bonded to cellular nucleic acids.

Recently the four diol epoxides **150**–**153** from fluoranthene have been prepared.<sup>73</sup> Whereas the standard methodology was successful for the



synthesis of **150** and **151**, **152** and **153** were prepared by a route utilizing stereoselective, directed epoxidation. The diol epoxides **150** and **151** are

<sup>72</sup> D. R. Boyd, K. A. Dawson, G. S. Gadaginamath, J. G. Hamilton, J. F. Malona, and N. D. Sharma, *J.C.S. Perkin I*, 94 (1981).

<sup>73</sup> W. H. Rastetter, R. B. Nachbar, S. Russorodriguez, R. V. Wattley, and W. G. Thilly, *J. Org. Chem.* **47**, 4873 (1982).

predicted to be more reactive than **152** and **153**. This is borne out in terms of relative mutagenicity of the diol epoxides in a bacterial screen.

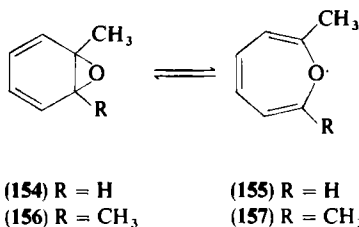
### III. Arene Oxide–Oxepin Valence Tautomerism

One of the important features of the structure and reactivity of arene oxides is the possibility of their involvement in valence tautomerism with the oxepin system. In benzene oxide (**86**) the two  $\pi$  bonds and the C—C  $\sigma$  bond undergo facile disrotatory electrocyclic reaction to give a  $6\pi$ -oxepin system (**96**).

On the other hand, certain arene oxides do not undergo this valence tautomerism. Thus the arene oxide formulation can fully represent the structure and reactivity of a compound, but in other cases the oxepin form alone fits the structure and reactivity.

In the case of benzene, a number of epoxides are known, e.g., mono-, di-, and triepoxides. All undergo interesting electrocyclic reactions. Benzene epoxide itself exists as a valence tautomer of **86** and **96**.<sup>8</sup> The enthalpy difference between the two forms is 1.7 kcal/mol. The activation energies for forward and reverse reactions are 9.1 and 7.2 kcal/mol, respectively. At room temperature the rate of exchange is so fast that the NMR spectrum is the average of chemical shifts that are due to protons represented by structures **86** and **96**.

Substitution of methyl groups on the oxirane ring tilts the stability of the tautomers in favor of oxepin. Thus 1-methylbenzene oxide (**154**) exists as 2-methyloxepin (**155**), in rapid equilibrium with the benzene oxide tautomer **154**.<sup>74</sup> The  $\Delta H$  has been calculated as  $0.4 \pm 0.02$  kcal/mol, i.e., 1.3 kcal/mol



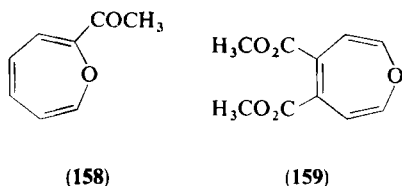
lower than that of the parent system. The activation energies for the forward and reverse reactions are 9.2 and 8.7 kcal/mol, respectively. Thus the introduction of the methyl group stabilizes the oxepin form with respect to the oxide form. At  $-113^\circ\text{C}$ , the molar ratio of **154** and **155** is 3:7.

The same trend is continued for the 1,2-dimethylbenzene oxide (**156**)–2,7-dimethyloxepin (**157**) system.<sup>8</sup> The oxepin is so strongly stabilized that the

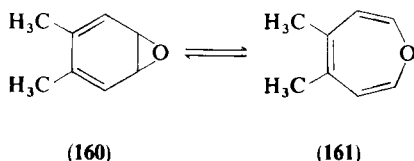
<sup>74</sup> H. Gunther, R. Schubart, and E. Vogel, *Z. Naturforsch. B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **22B**, 25 (1967).

concentration of the benzene oxide component (**156**) is below the spectroscopic detection limits ( $< 5\%$ ). The NMR spectrum of the compound does not show signs of line broadening even at  $-110^\circ\text{C}$ . The relative stability of **157** is ascribed to either the hyperconjugative stabilization of this form by the methyl groups or the steric crowding and destabilization of the benzene oxide.

When attempts were made to prepare **102**, a red brown 2-acetyloxepin (**158**) was obtained. The NMR spectrum showed very little change with temperature and was consistent only with oxepin structure **158**.<sup>8</sup>



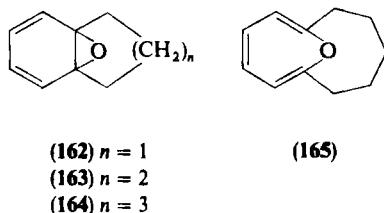
4,5-Dimethoxycarbonylbenzene oxide (**98**) exists in equilibrium with the oxepin form (**159**), the latter predominating at equilibrium at ambient temperature.<sup>8</sup> The NMR spectrum shows temperature dependence, indicating that a considerable amount of the oxide tautomer exists at equilibrium. 4,5-Dimethylbenzene oxide (**160**) also exists in equilibrium with its corresponding oxepin tautomer (**161**).<sup>8</sup>



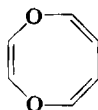
In these 4,5-substituted compounds mentioned, the arene oxide is the low-energy component over the range from room temperature to  $-65^\circ\text{C}$ .

A series of bicyclic arene oxides having three-, four-, and five-membered methylene bridges at the oxirane ring have been prepared.<sup>8</sup> The compound having a bridge with three carbon atoms, indane 8,9-oxide (**162**), is shown to exist in the norcaradiene form by comparison of relevant spectra. Similarly, in the case of the compound having a four-membered methylene bridge, tetraline 9,10-oxide (**163**), an assignment was made in favor of an arene oxide structure on the basis of its UV spectrum. However, in the case of the compound bearing a five-membered methylene bridge, the compound is orange in color, indicating the presence of oxepin, and all of the spectral characteristics indicate dynamic equilibrium between arene oxide **164** and oxepin **165**.

A number of variously substituted benzene epoxides have been reported. Their valence tautomeric behavior cannot be described with certainty because of inadequate information.



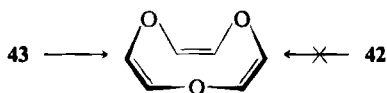
In the crystalline state *syn*-benzene diepoxide exists only as benzene diepoxide **55** at room temperature. However, on heating it undergoes symmetry allowed  $\pi 2_s + \sigma 2_s + \sigma 2_s$  cycloreversion to 1,4-dioxocin (**166**).<sup>58</sup>



(166)

At 60°C in benzene (but not in carbon tetrachloride) **166** undergoes valence tautomerism. At 60°C, the relative amounts of **55**:**166** are 5:95.<sup>32</sup> The conversion of **55** to **166** has an activation energy of 27 kcal/mol ( $A = 7.1 \times 10^{13}$ ), and the reverse reaction (**166** to **55**) has an activation energy of ~25 kcal/mol ( $A = 3.2 \times 10^{11}$ ). Substitution of bromine in position 1 of **55** shifts the equilibrium toward the oxide as compared to the unsubstituted derivative.<sup>58</sup>

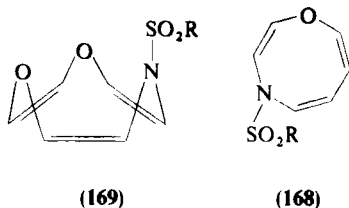
*syn*-Benzene triepoxide (**43**) undergoes orbital symmetry allowed electrocyclic transformation to *cis,cis,cis*-1,4,7-trioxacyclononatriene (**167**) at 200°C. On the other hand, the *anti*-benzene triepoxide (**42**) is thermally stable and heating for several hours at 200°C or pyrolysis at 400–500°C does not bring about any electrocyclic reaction.<sup>26</sup>



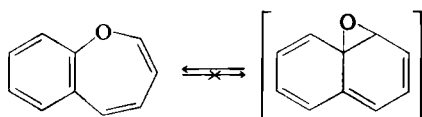
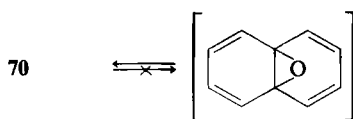
(167)

Analogous *syn*-epoxides **49** and **50** undergo electrocyclic reactions to give the corresponding 4*H*-1,4-oxazocins (**168**) and 7*H*-1,4,7-dioxazocins (**169**), respectively. The activation energies of these reactions have been measured, and it is suggested that the reactions are concerted.<sup>29</sup>

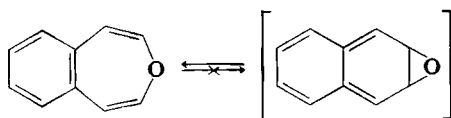
All four arene oxides derivable from naphthalene have been prepared, and their structures are sufficiently well defined. None of them shows valence tautomerism. They exist exclusively either in the oxepin or arene oxide forms.



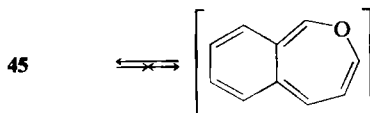
In the cases of **170**, **171**,<sup>75-79</sup> and **45**, the resonance energy of the benzene moiety ( $\sim 39$  kcal) trips the stability order irretrievably on the side of oxepin in the first two cases and in favor of arene oxide in the case of **45**. Tautomerism, which ordinarily is manifested with systems having small energy differences, is therefore ruled out. However, in the case of the 9,10-oxide this limitation does not exist, but even so, the compound exists only in the oxepin form (**70**),<sup>8</sup> possibly because of a very high strain on the oxirane ring in the epoxy form.



(170)



(171)



<sup>75</sup> K. Dimroth and G. Pohl, *Angew. Chem.* **73**, 436 (1961).

<sup>76</sup> K. Dimroth, G. Pohl, and H. Follman, *Chem. Ber.* **99**, 634 (1966).

<sup>77</sup> G. R. Ziegler and G. S. Hammond, *J. Am. Chem. Soc.* **90**, 513 (1968).

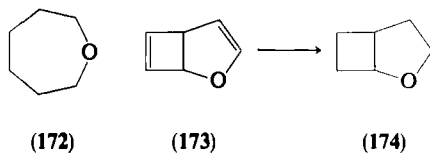
<sup>78</sup> G. R. Ziegler, *J. Am. Chem. Soc.* **91**, 446 (1969).

<sup>79</sup> A. M. Jeffrey and D. M. Jerina, *J. Am. Chem. Soc.* **94**, 4048 (1972).

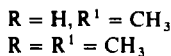
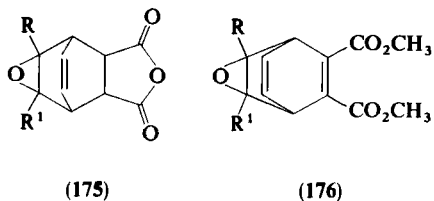
In both *syn*- and *anti*-diepoxides of naphthalene, the existence of either valence tautomerism or thermal electrocyclic reaction has not been reported.

The bulk of the polycyclic arene oxides do not show a dynamic equilibrium with the oxepin valence tautomer. This is particularly true for the K-region arene oxides, which exist exclusively in the arene oxide forms. A number of oxepins exist only as such and do not show physical, spectroscopic, or chemical reactivities corresponding to the arene oxide form, e.g., **70**, **170**, **171**, etc. Tautomeric behavior of some representative arene oxide-oxepin pairs is summarized in Table I.<sup>8</sup>

In the case of monocyclic benzene oxides, independent of whichever isomer is predominant, most of the chemical reactions are of the oxide form. The exceptions are only hydrogenation and photochemical reactions. Hydrogenation of benzene oxide catalyzed by Pd-C furnishes nearly 70% of oxepane **172** along with cyclohexanol and some unidentified products.<sup>8</sup> Similarly, photochemical reaction of **86**  $\rightleftharpoons$  **96** yields 2-oxabicyclo[3.2.0]hepta-3,6-diene (**173**). The structure of **173** was confirmed by hydrogenation to 2-oxabicyclo[3.2.0]heptane (**174**).<sup>8</sup>



Both the monomethylbenzene oxide **153**–**155**, which exists in dynamic equilibrium with a predominant oxepin component, and 2,7-dimethyloxepin (**157**), with almost no benzene oxide component (**156**), in equilibrium at ambient temperature, react with maleic anhydride and dimethyl acetylenedicarboxylate to give the Diels-Alder adducts **175** and **176**, respectively, resulting from reaction with the oxide form.<sup>8</sup>



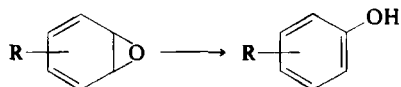
The formation of phenols by opening the epoxide ring, spontaneously or by acid catalysis, is characteristic of an arene oxide form, as is shown below by monocyclic oxepins whether or not benzene oxide is present in substantial

TABLE I  
ARENE OXIDE-OXEPIN TAUTOMERISM

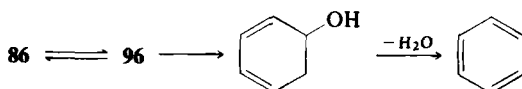
Arene oxide A	Oxepin O	Solvent	Temperature °C	Composition (%)	
				A	O
Benzene oxide	Oxepin	Isooctane H <sub>2</sub> O:CH <sub>3</sub> OH (85:15)	25	30	70
1-2-Dimethylbenzene oxide	2,7-Dimethyloxepin	CS <sub>2</sub> , CCl <sub>4</sub>	25	90	10
1-Acetylbenzene oxide	2-Acetyloxepin	—	25	5	95
				Below detection limits	100
4,5-Dimethylbenzene oxide	4,5-Dimethyloxepin	—	—65	100	Almost nil
Indane 8,9-oxide	—	—	—	100	0
Tetraline 9,10-oxide	—	—	—	100	0
<i>syn</i> -Benzene dioxide	Dioxocin	C <sub>6</sub> H <sub>6</sub>	60	5	95
1-Bromobenzene oxide	2-Bromodioxocin	CCl <sub>4</sub>	77	35	65



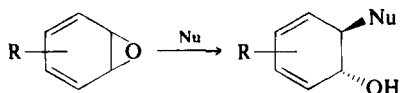
amounts at equilibrium.<sup>80</sup> Also equilibrium mixture  $86 \rightleftharpoons 96$ , on reaction with



lithium aluminum hydride, produces cyclohexa-1,2-dien-5-ol, which is immediately converted to benzene by dehydration. This reaction is characteristic only of arene oxides.<sup>8</sup> Nucleophiles derived from sulfur, nitrogen, oxygen, and



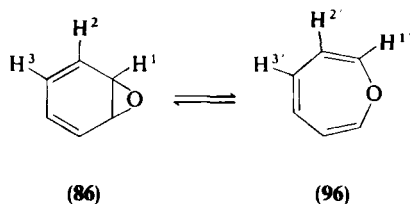
organometallic compounds react only with the arene oxide of the oxide-oxepin tautomeric system.<sup>8</sup>



#### IV. Structural Features

NMR spectroscopy has been extremely useful in determining the equilibrium position between arene oxides and oxepin forms. The hydrogens of the oxirane ring show chemical shifts ranging from  $\delta$  3 to  $\delta$  5, mostly centered around  $\delta$  4.4–5.0. There is a considerable downfield shift of the oxirane ring protons compared to ethylene oxide oxirane-ring protons. The largest shift is observed where the hydrogen is hindered as in the case of H4 of 48.

In the cases of benzene epoxide and its congeners, cooling the sample to  $-113^\circ\text{C}$  brings about a separation of the peaks of the two tautomers as a result of the slowing down of the rapid transformation that ordinarily takes place at ambient temperature. Thus in the case of  $86 \rightleftharpoons 96$  the NMR spectrum



at  $-127^\circ\text{C}$  shows the following signals: H1 at  $\delta$  4.0, H1' and H2' at  $\delta$  5.6, and H3, H3', and H2 at  $\delta$  6.4.<sup>8</sup> The chemical-shift values of oxirane-ring protons of some arene oxides are given in Table II.<sup>81–86</sup>

TABLE II  
CHEMICAL SHIFT VALUES OF OXIRANE PROTONS OF SOME ARENE OXIDES

Arene oxide	Chemical shift (ppm)	Reference
Benzene oxide	4.0	8
1-Carboxylbenzene oxide	5.96	81
1-Formylbenzene oxide	6.01	82
1-Hydroxymethylbenzene oxide	5.03	82
1-(2-Hydroxy-2-propyl) benzene oxide	5.03	82
1-Cyanobenzene oxide	5.99	83
1-Methoxycarbonylbenzene oxide	5.94	81
3- <i>t</i> -Butoxycarbonylbenzene	4.29 (H1),	55
1,2-oxide	4.91 (H2)	
4-Methyl-1-methoxycarbonyl-benzene oxide	5.87	81
Naphthalene 1,2-oxide	4.25 (H1),	57
	3.85 (H2)	
<i>syn</i> -Naphthalene 1,2:3,4-dioxide	3.96 (H1, H4),	30
	3.89 (H2, H3)	
<i>anti</i> -Naphthalene 1,2:3,4-dioxide	3.94 (H1, H4),	30
	3.66 (H2, H3)	
Phenanthrene 1,2-oxide	4.25 (H2),	31
	4.67 (H1)	
Phenanthrene 3,4-oxide	4.07 (H3),	31
	5.02 (H4)	
Phenanthrene 9,10-oxide	4.40	34
2-Dodecylphenanthrene 9,10-oxide	4.5 (H9, H10)	15
3-Acetylphenanthrene 9,10-oxide	4.5 (H9, H10)	84
9-Acetylphenanthrene 9,10-oxide	4.48	15
1-Azaphenanthrene 5,6-oxide	4.48	15
3-Azaphenanthrene 5,6-oxide	4.57	15
1,10-phenanthroline 5,6-oxide	4.55	15
Pyrene 4,5-oxide	4.83	18
Benz[ <i>a</i> ]anthracene 10,11-oxide	4.18 (H10),	81
	4.71 (H11)	
Benz[ <i>a</i> ]anthracene 5,6-oxide	4.7 and 4.8	85
7,12-Dimethylbenz[ <i>a</i> ]anthracene 5,6-oxide	4.27 and 4.68	17
Chrysene 3,4-oxide	4.31 (H3),	86
	5.32 (H4)	

<sup>80</sup> J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia* **28**, 1129 (1972).

<sup>81</sup> D. R. Boyd and G. A. Berchtold, *J. Am. Chem. Soc.* **101**, 2470 (1979).

<sup>82</sup> H. S.-I. Chao and G. A. Berchtold, *J. Am. Chem. Soc.* **103**, 898 (1981).

<sup>83</sup> H. S.-I. Chao and G. A. Berchtold, *J. Org. Chem.* **46**, 813 (1981).

<sup>84</sup> G. W. Griffin, S. K. Satra, N. E. Brightwell, K. Ishikawa, and N. S. Bhacca, *Tetrahedron Lett.*, 1242 (1976).

<sup>85</sup> R. G. Harvey, S. H. Goh, and C. Cortez, *J. Am. Chem. Soc.* **97**, 3469 (1975).

<sup>86</sup> D. R. Boyd, M. G. Burnett, and R. M. E. Greene, *J.C.S. Perkin I*, 595 (1983).

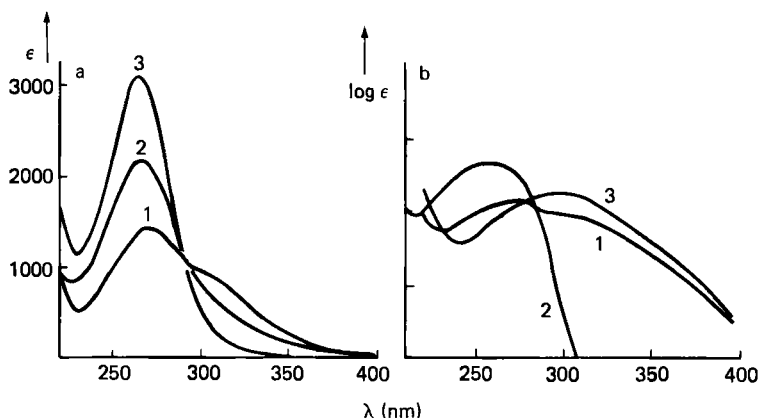


FIG. 1. (a) UV spectrum of **86**  $\rightleftharpoons$  **96** (1) in isooctane, (2) in methanol, and (3) in water-methanol (85:15). (b) UV spectra in isooctane: (1) **86**  $\rightleftharpoons$  **96**; (2) **162**; (3) **157**.

For oxirane rings an IR absorption around  $890\text{ cm}^{-1}$  is characteristic. This is also observed in the case of K-region epoxides and can be used for diagnostic purposes, but it is not sensitive enough to provide detailed structural information. The oxepins ordinarily do not show this band. Ultraviolet spectroscopy has been invaluable in studying the dynamic equilibrium between the arene oxides and oxepins. The solvent variation of UV spectra has also been exploited very effectively.<sup>8</sup>

Compound **162** is colorless and in isooctane possesses a UV spectrum of the cyclohexa-1,3-diene type, with a maximum at  $258\text{ nm}$  ( $\epsilon = 4900$ ). The reference for the oxepin structure is **157**, which has a broad band at  $297\text{ nm}$  ( $\epsilon = 1800$ ) in isooctane. When the solvent polarity is increased or the temperature is lowered, the equilibrium shifts clearly from the oxepin to the epoxide form.<sup>8</sup>

From the analysis of the coupling constants of olefinic protons in conjunction with the UV spectrum of 2,7-pentamethylene-bridged oxepin, it has been found that the oxepin is in equilibrium with its mirror image in a nonplanar boat form [see Fig. 1, Eq. (4)].<sup>8</sup>

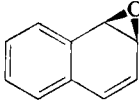
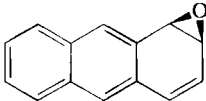
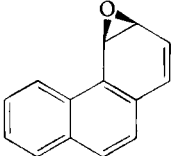
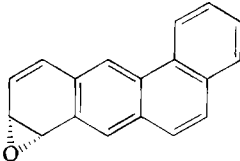
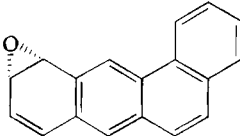
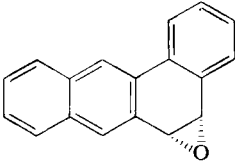
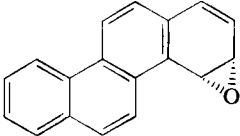


The configurational data of some arene oxides are collected in Table III.

The molecular structures of **30** and **1** have been determined by X-ray crystallography.<sup>87</sup> Compound **1** is approximately planar, excluding the

<sup>87</sup> J. P. Glusker, H. L. Carrell, D. E. Zacharias, and R. G. Harvey, *Cancer Biochem. Biophys*, **1**, 43 (1974).

TABLE III  
CONFIGURATION AND SPECIFIC ROTATIONS OF ARENE OXIDES

Structure	Configuration	Rotation	Reference
	(1 <i>R</i> , 2 <i>S</i> )	+ 149	67
	(1 <i>R</i> , 2 <i>S</i> )	+ 214	65
	(3 <i>S</i> , 4 <i>R</i> )	+ 4 → 0 (spontaneous racemization)	70
	(8 <i>S</i> , 9 <i>R</i> )	− 115	72
	(10 <i>S</i> , 11 <i>R</i> )	+ 383	71
	(5 <i>S</i> , 6 <i>R</i> )	+ 36 (optical purity ~ 30%)	71
	(3 <i>S</i> , 4 <i>R</i> )	+ 224	86

oxygen and hydrogen atoms of the epoxide ring, whereas **30** is nonplanar, with an angle of  $35^\circ$  between the two most distant rings. The nonplanarity is found in the parent compound of **30** and is the result of steric repulsion between the  $12\text{-CH}_3$  group and the ring. The epoxide oxygen of one molecule packs nearest to C-7 of another, indicating the probable site of maximum positive charge in the crystal lattice.

## V. Reactions of Arene Oxides

### A. AROMATIZATION REACTIONS

Rapid isomerization to the isomeric phenol is probably the most characteristic and pervasive feature of arene oxide chemistry. Benzene oxide (**86**) has a half-life of less than 2 min, whereas naphthalene 1,2-oxide (**45**) has a half-life of over 4 min at pH 7 ( $30^\circ\text{C}$ , 1 M KCl)<sup>6</sup>. The half-life of phenanthrene 9,10-oxide **1** is about 10 min, and those for phenanthrene 1,2-(**47**) and 3,4-oxides (**48**) are 4 and 2.5 sec respectively.<sup>2</sup> Thus it can be seen that oxide **1** is much more stable than other isomeric epoxides. The stability of the arene oxides for spontaneous as well as acid-catalyzed ring-opening reactions very much depends on the position of the epoxide ring in a polycyclic hydrocarbon. Epoxides derived from positions having very high  $\pi$ -electron density, i.e., the K-region of the aromatic hydrocarbons, e.g., **1**, differ markedly in stability, as determined by the ease of ring opening from the congeners derived from lesser  $\pi$ -electron density positions. Detailed study of the reactivity confirms the existence to some extent of dichotomy of reaction patterns of K- and non-K-region arene oxides.

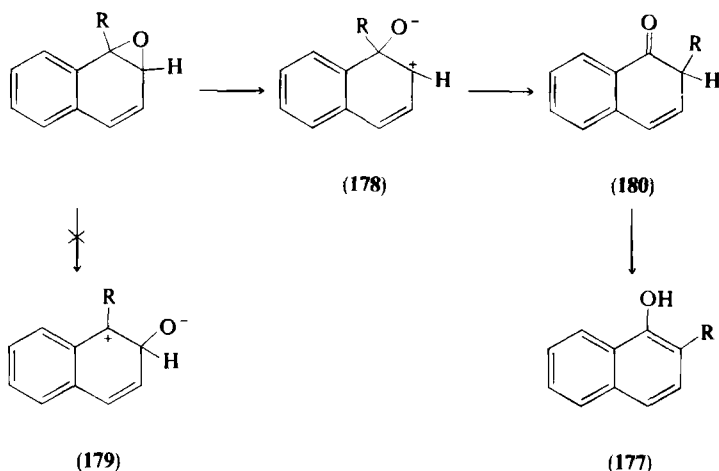
On solvolysis, **1** gives three products: 9-phenanthrol and *cis*- and *trans*-9,10-dihydro-9,10-dihydroxyphenanthrene.<sup>88</sup> On the other hand, **47** and **48** give mainly 1-phenanthrol and 4-phenanthrol, respectively, along with minor amounts (3–24%) of other isomeric phenanthrols.<sup>89</sup> Similarly, **86** gives phenol and **45** gives only 1-naphthol.<sup>90</sup> However, in acid approximately 10% of 2-naphthol is formed. In all of the latter cases there is no evidence for the formation of dihydrodiols.

<sup>88</sup> P. Y. Bruice, T. C. Bruice, P. M. Dansette, H. G. Selander, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.* **98**, 2965 (1976).

<sup>89</sup> P. Y. Bruice, T. C. Bruice, H. G. Selander, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.* **96**, 6814 (1974).

<sup>90</sup> G. J. Kasperek and T. C. Bruice, *J. Am. Chem. Soc.* **94**, 198 (1972).

The ring-opening reaction in an overwhelmingly large number of cases is characterized by two features: (a) the oxirane ring opens only in one direction, and (b) the group located on the ring moves to the neighboring position (NIH shift). In the following example, only the 1-naphthol (177) is formed and not the 2-naphthol. These features have been ascribed to the large differences in the relative stabilities of the two possible zwitterionic species, e.g., 178 and 179 and the intermediacy of keto tautomer 180.



R = D, T, Br, Ph, etc.

Detailed work with arene oxides, especially those bearing alkyl substituents on the oxirane ring revealed the operation of two additional phenomena: (c) "solvent trapping," and (d) "oxygen walk."

In the case of 1,4-dimethylbenzene epoxide (181), incursion of intermediates like 1,4-dimethyl-1,4-dihydroxydihydrobenzene (182)<sup>91,92</sup> or intermediates like 4,8- and 4,5-indane oxides (183 and 184), respectively, by oxygen walk<sup>8,93-96</sup> does not allow prediction of the product of epoxide opening on

<sup>91</sup> G. J. Kasperek, T. C. Bruice, N. Kaubisch, and D. M. Jerina, *J. Am. Chem. Soc.* **94**, 7876 (1972).

<sup>92</sup> H. Yagi, D. M. Jerina, G. J. Kasperek, and T. C. Bruice, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 1985 (1972).

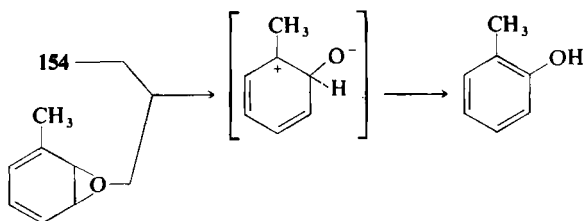
<sup>93</sup> J. W. Daly, D. M. Jerina, H. Ziffer, B. Witkop, F. G. Klarner, and E. Vogel, *J. Am. Chem. Soc.* **92**, 702 (1970).

<sup>94</sup> P. Y. Bruice, G. J. Kasperek, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.* **95**, 1673 (1973).

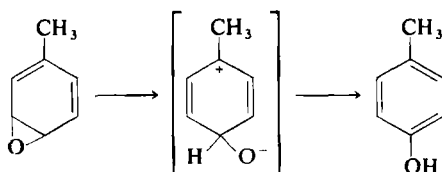
<sup>95</sup> G. J. Kasperek, P. Y. Bruice, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.* **95**, 6041 (1973).

<sup>96</sup> D. M. Jerina, N. Kaubisch, and J. W. Daly, *Proc. Natl. Acad. Sci. U.S.A.* **68**, 2545 (1971).

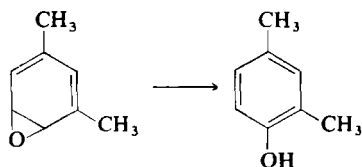
the simple considerations mentioned above. In the isomeric toluene oxides **154**, **185**, and **186**,<sup>96</sup> only *o*- and *p*-cresols are formed and no *m*-cresol. The same pattern is repeated<sup>80</sup> for **187** and **188**. All of these products are derived by the involvement of the more stable of the two possible zwitterions.



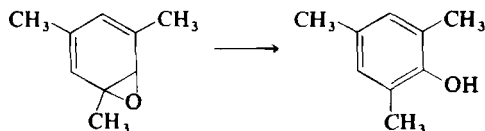
(185)



(186)



(187)

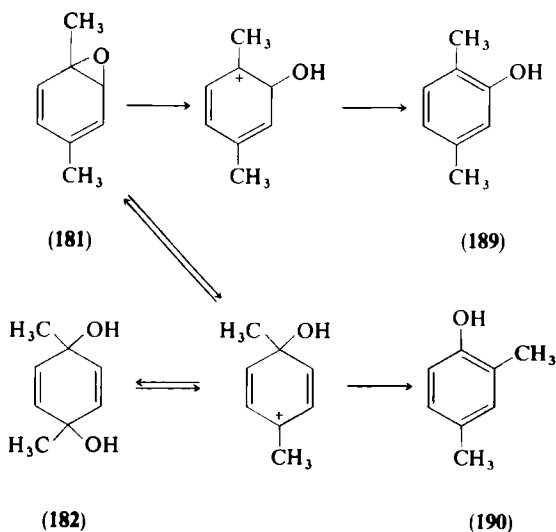


(188)

### 1. Solvent Trapping

Isomerization of **181** has been shown to lead to 2,5- and 2,4-dimethylphenols (**189** and **190**), respectively. At low acidity, 13% of **189** and 87% of **190** are formed. The rate of decomposition of arene oxide is the same as the rate of formation of these products. Under stronger acidic conditions the product ratio changes to 54% of **189** and 46% of **190**. These discrepancies have been shown to arise from the accumulation of intermediate **182**.<sup>91,92</sup>

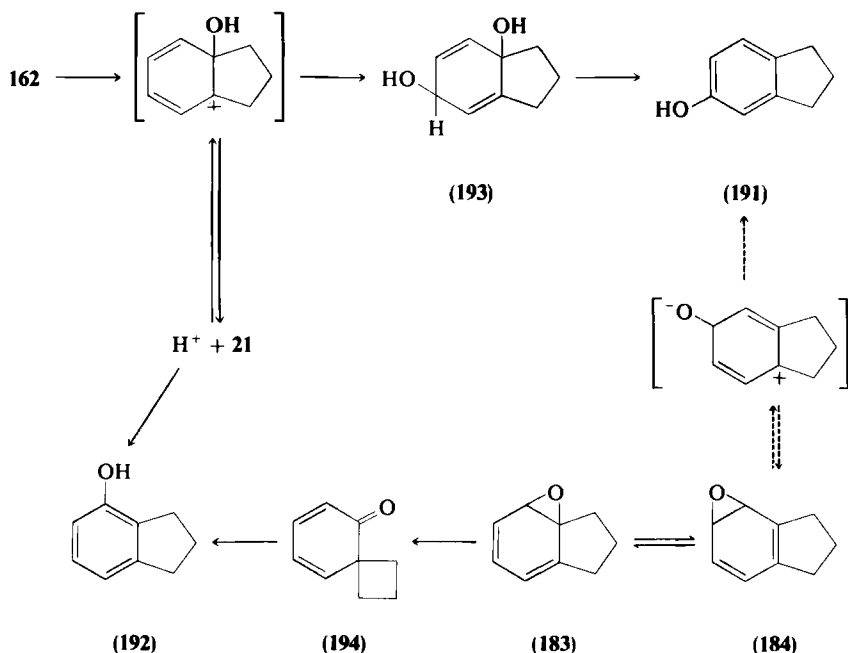
The free energies of activation associated with different transition states differ only by about 1.5 kcal. Methyl migration is partially rate determining, but there is no analogous H migration as found with **1** and **2**. Formation of intermediates like **182** by reaction of the reactive zwitterion with the solvent has been designated as solvent trapping.



## 2. Oxygen Walk

Isomerization of **162** gives 5-indanol (**191**) and 4-indanol (**192**).<sup>94,95</sup> Formation of **191** is attributed to solvent trapping. In this case the rate of disappearance of the oxide is not proportional to the rate of appearance of the phenolic products. Evidence for the accumulation of intermediate **193** is provided. On the other hand, formation of **192** results from two independent paths: through a spirolactone (**194**) and through opening of the epoxide ring to a zwitterion and its closing to give an arene oxide different from the original starting material. This process repeating itself leads to migration of oxygen from the bridgehead position to the position linking 4 and 5. This rearrangement involving the conversion of one arene oxide to another with the oxygen position shifted by a number of carbon atoms has been described as the oxygen walk. This oxygen walk phenomenon is solvent dependent. The percentage of reaction going through this pathway in the case of **162** increases on going from 50% dioxane–water to a more polar medium like water.<sup>2</sup>





### 3. NIH Shift

During a study of the hydroxylation of 4-T-phenylalanine (195) to tyrosine (196), a surprising result was obtained. The tyrosine retained 95% tritium in the position next to the hydroxy group. Similar retention of substituents like deuterium, methyl, or chloro, came to be recognized as a general feature<sup>97-99</sup> in the hydroxylation of aromatic rings by mixed-function oxygenases (see Table IV<sup>100-109</sup>). This rearrangement was designated as the NIH (National

<sup>97</sup> G. Guroff and J. Daly, *Arch. Biochem. Biophys.* **122**, 212 (1967).

<sup>98</sup> G. Guroff, C. A. Reifsnyder, and J. Daly, *Biochem. Biophys. Res. Commun.* **24**, 720 (1966).

<sup>99</sup> L. Nover and M. Luckner, *FEBS Lett.* **3**, 292 (1969).

<sup>100</sup> J. Renson, J. Daly, H. Weissbach, B. Witkop, and S. Udenfriend, *Biochem. Biophys. Res. Commun.* **25**, 504 (1966).

<sup>101</sup> G. Guroff, K. Kondo, and J. Daly, *Biochem. Biophys. Res. Commun.* **25**, 622 (1966).

<sup>102</sup> J. Daly and G. Guroff, *Arch. Biochem. Biophys.* **125**, 136 (1968).

<sup>103</sup> E. R. Blakley, *Can. J. Microbiol.* **18**, 1247 (1972).

<sup>104</sup> R. L. Crawford, *J. Bacteriol.* **127**, 204 (1976).

<sup>105</sup> J. Daly, G. Guroff, S. Udenfriend, and B. Witkop, *Arch. Biochem. Biophys.* **122**, 218 (1967).

<sup>106</sup> D. M. Foulkes, *Nature (London)* **221**, 582 (1969).

<sup>107</sup> D. W. Russell, E. E. Conn, A. Sutter, and H. Grisebach, *Biochim. Biophys. Acta* **170**, 210 (1968).

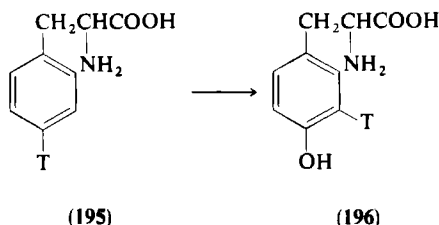
<sup>108</sup> J. Daly, D. Jerina, J. Farnworth, and G. Guroff, *Arch. Biochem. Biophys.* **131**, 238 (1969).

<sup>109</sup> J. Daly and D. Jerina, *Arch. Biochem. Biophys.* **134**, 266 (1969).

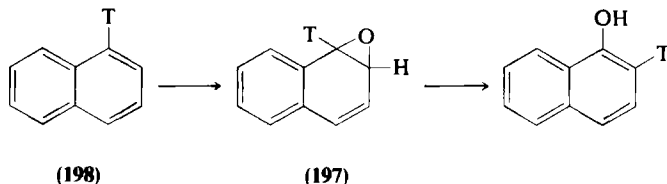
TABLE IV  
A SELECTED LIST OF ENZYME SYSTEMS THAT BRING ABOUT THE NIH SHIFT

Enzyme system or source	Substrate	Product	Percentage retention of deuterium	Reference
Tryptophan-5-hydroxylase (from mouse neoplastic mast cells)	5-T-L-Tryptophan	5-Hydroxy-4-T- L-tryptophan	85	100
Bacterial phenylalanine hydroxylase	<i>p</i> -Chlorophenyl- alanine	<i>m</i> -Chlorotyrosine	—	101
<i>Pseudomonas</i> and rat liver phenylalanine hydroxylase	4-Methylphenyl- alanine	<i>m</i> -Methyltyrosine	—	102
Extract of cells from bacterium PRL W19	4-Hydroxyphenyl- acetic acid	2,5-Dihydroxyphenylacetic acid	—	103
4-Hydroxybenzoate- 1-hydroxylase (?)	4-Hydroxybenzoic acid	2,5-Dihydroxybenzoic acid	—	104
Liver microsomes	4-T-Amphetamine	3-T-4-Hydroxyamphetamine	80-90	105
<i>In vivo</i> metabolism in rats	2-(4'-chlorophenyl)- thiazole-4- acetic acid (an antiinflam- matory drug)	2-(3'-Chloro-4'-hydroxy)- thiazole-4-acetic acid.	—	106
<i>In vitro</i> cell free microsomes (from pea seedlings and <i>Catalpha hybrida</i> leaf discs	4-T-Cinnamic acid	3-T-4-Hydroxycinnamic acid	85-90	107
Liver microsomes	4-D-4'-fluorobiphenyl	3-D-4-Hydroxy-4'- fluorobiphenyl	63	108
Liver microsomes	2-D-Anisole	3-D-2-Hydroxyanisole	60	109

Institute of Health) shift.<sup>80,110,111</sup> Originally, the term NIH shift was used as a phenomenological description of the consequence of hydroxylation of aromatic compounds by mixed-function oxygenases. These enzymes catalyze the oxidation of aromatic substrates by deriving oxygen from molecular oxygen and not from water.<sup>80,110,111</sup> Later studies narrowed the term to include arene oxide involvement.<sup>80</sup>



The mechanism of the NIH shift was not clearly understood until naphthalene 1,2-oxide (197) was isolated in the metabolism of 1-T-naphthalene (198) with hepatic monooxygenases; the oxide then rearranges to 1-naphthol with migration of tritium from the 1- to the 2-position.<sup>112,113</sup>



On the basis of these observations, the NIH shift was attributed to a chemical sequence involving oxidation of the aromatic ring to an arene oxide, opening of the oxide to an ionic intermediate, and finally rearrangement to a phenol with migration of a substituent. When appropriately labeled arene oxides were prepared, shifts to the extent of about 95% were observed.

Inorganic reagents like chromyl chloride, chromyl acetate in carbon tetrachloride,<sup>114</sup> as well as peroxytrifluoroacetic acid<sup>115,116</sup> are believed to

<sup>110</sup> B. Witkop, in "Current Topics in Biochemistry" (C. B. Anfinsen and A. N. Schechter, eds.), p. 109. Academic Press, New York, 1974.

<sup>111</sup> G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop, and S. Udenfriend, *Science* **157**, 1524 (1967).

<sup>112</sup> D. M. Jerina, J. W. Daly, B. Witkop, P. Z. Nirenberg, and S. Udenfriend, *J. Am. Chem. Soc.* **90**, 6525 (1968).

<sup>113</sup> D. M. Jerina, J. W. Daly, B. Witkop, P. Z. Nirenberg, and S. Udenfriend, *Biochemistry* **9**, 147 (1970).

<sup>114</sup> K. B. Sharpless and T. C. Flood, *J. Am. Chem. Soc.* **93**, 2316 (1971).

<sup>115</sup> D. M. Jerina, J. W. Daly, W. Landis, B. Witkop, and S. Udenfriend, *J. Am. Chem. Soc.* **89**, 3347 (1967).

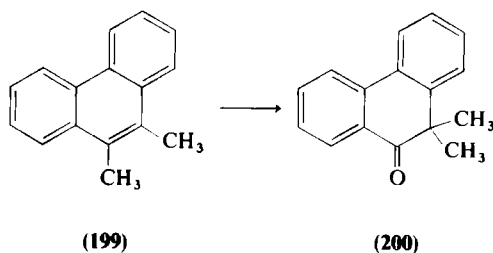
<sup>116</sup> D. M. Jerina, J. W. Daly, and B. Witkop, *Biochemistry* **10**, 366 (1971).

TABLE V  
CHEMICAL OXIDANTS THAT CAUSE THE NIH SHIFT AND  
ARYL HYDROXYLATIONS

Oxidant	Percentage retention of deuterium in 4-anisole	Reference
9-Diazofluorene, O <sub>2</sub> , <i>hν</i>	16	117
N <sub>2</sub> O, <i>hν</i>	25	63, 118
<i>t</i> -Butyl hydroperoxide, Mo(CO) <sub>6</sub>	58	63, 119
Dimethylaniline <i>N</i> -oxide, <i>hν</i>	20	63
Pyridine <i>N</i> -oxide, <i>hν</i>	45	63
Pyridiazine <i>N</i> -oxide, <i>hν</i>	34	63
Pyrazine <i>N</i> -oxide, <i>hν</i>	52	63
Peroxyacid	—	115, 116
Sn(II), O <sub>2</sub>	—	120
CrO <sub>2</sub> (OAc) <sub>2</sub>	—	114

function through epoxidation and are considered to be models for oxygenases (see Table V<sup>117-120</sup>).

Also, 9,10-dimethylphenanthrene (199) on oxidation with Cr(V)–phenanthroline complex has been shown to give 10,10-dimethyl-9-phenanthrone (200).<sup>121</sup>



The NIH shift has been recognized to be so general that whenever a 1,2-shift occurs in aromatic hydroxylation reactions, it is assumed that arene oxides are involved. This need not be so. That the 1,2-shift could take place without the

<sup>117</sup> G. A. Hamilton and J. R. Giacin, *J. Am. Chem. Soc.* **88**, 1585 (1966).

<sup>118</sup> R. J. Cvetanovic, *Adv. Photochem.* **1**, 115 (1963).

<sup>119</sup> M. N. Sheng and J. C. Zajackin, *Adv. Chem. Ser.* **76**, 418 (1968).

<sup>120</sup> D. M. Jerina, J. W. Daly, and B. Witkop, in "Biogenic Amines and Physiological Membranes in Drug Therapy" (J. M. Biel and L. G. Abood, eds.), Part B, p. 413. Dekker, New York, 1971.

<sup>121</sup> M. V. Bhatt and G. S. Shirwaiker, unpublished results.

TABLE VI  
RATE CONSTANTS FOR THE ACID-CATALYZED DECOMPOSITION OF  
K-REGION ARENE OXIDES<sup>a</sup>

Compound	$k_{\text{obs}}$ (sec <sup>-1</sup> )	Relative rate
Phenanthrene 9,10-oxide	$1.9 \times 10^{-4}$	1.0
Pyrene 4,5-oxide	$1.71 \times 10^{-4}$	0.9
Benz[a]anthracene 5,6-oxide	$3.99 \times 10^{-4}$	2.1
Benzo[a]pyrene 4,5-oxide	$3.61 \times 10^{-4}$	1.9
2-Methoxyphenanthrene 9,10-oxide	$3.42 \times 10^{-4}$	1.8
3-Methoxyphenanthrene 9,10-oxide	$3.8 \times 10^{-3}$	> 20
2-Methoxycarbonylphenanthrene 9,10-oxide	$0.17 \times 10^{-4}$	0.09
3-Methoxycarbonylphenanthrene 9,10-oxide.	$0.11 \times 10^{-4}$	0.06

<sup>a</sup> In aqueous acetone, pH 2.3; see ref. 24.

involvement of arene oxides in highly acidic media has been shown during oxidation of aromatic substrates by single electron oxidants.<sup>122-125</sup>

Because of the great biological significance of arene oxides and the large number of different reactions they could undergo in water and with animal tissues, detailed quantitative studies have been carried out with a variety of arene oxides in aqueous medium. (See Table VI).

It is convenient to consider the reactions of K-region and non-K-region epoxides separately. Historically, K-region hydrocarbons and the arene oxides have been associated with carcinogenesis. Formation of K-region epoxides ordinarily reduces the aromatic resonance of the parent hydrocarbon to a much lesser extent than non-K-region arene oxides. Considering stability in aqueous media and the nature of product distributions during solvolysis, they differ from their analogs.

Detailed pH-rate profiles with pH in the range of 1 to 14 for the reaction of 1 in aqueous solution are available<sup>88</sup> (see Fig. 2). Between pH 2 and 7, two types of reactions take place concurrently. The ring opening is catalyzed by

<sup>122</sup> M. Periasamy and M. V. Bhatt, *Synthesis*, 330 (1977).

<sup>123</sup> M. Periasamy and M. V. Bhatt, *Tetrahedron Lett.*, 2357 (1977).

<sup>124</sup> M. Periasamy and M. V. Bhatt, *Tetrahedron Lett.*, 4561 (1978).

<sup>125</sup> G. A. Bhat, M. Periasamy, and M. V. Bhatt, *Tetrahedron Lett.*, 3097 (1979).

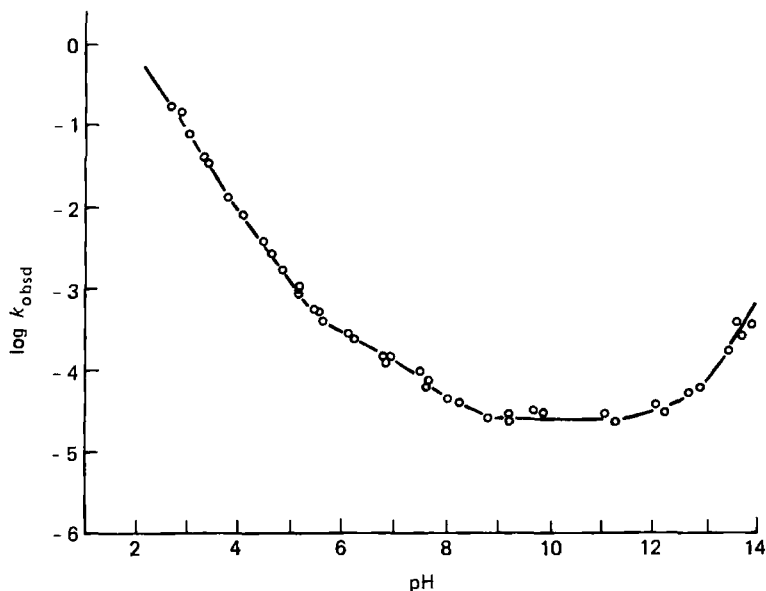
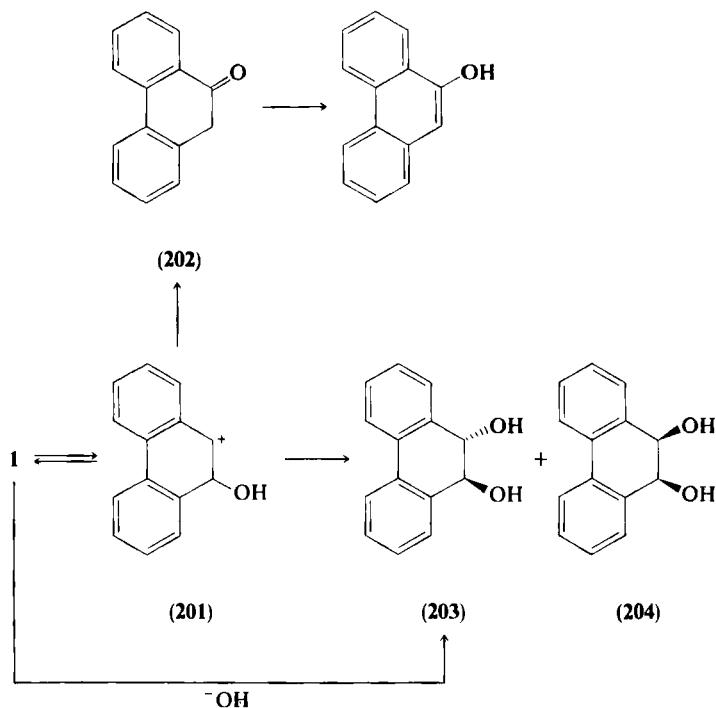


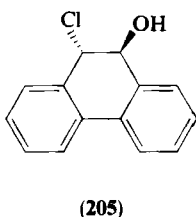
FIG. 2. Log  $k_{\text{obsd}}$  versus pH profile for the disappearance of phenanthrene 9,10-oxide (**1**) ( $\text{H}_2\text{O}$ ,  $30^\circ\text{C}$ ,  $\mu = 1.0$ ).

$\text{H}_3\text{O}^+$  and by water. Up to pH 7, both pathways give carbocation **201**. The carbocation itself can undergo three types of reactions: (a) the NIH shift to give ketone **202**, which enolizes to 9-phenanthrol; (b) reaction with water from the side trans to the hydroxyl group to give the *trans*-glycol **203**; and (c) reaction with water from the cis side to give the *cis*-glycol **204**. The proof for this common intermediate (**201**) was very convincingly provided by the fact that from pH 1 to 8 the product ratios remained constant at 75% of 9-phenanthrol, 18% of **203**, and 7% of **204**. Between pH 5 and 7 the reaction was subject to general acid catalysis and below pH 5 by  $\text{H}_3\text{O}^+$  catalysis. From pH 8.5 to about 11.5 the arene oxide was subject to nucleophilic attack by water molecules and above pH 11.5 by nucleophilic attack by  $\text{OH}^-$ . This mechanism is again supported by the fact that the product obtained in these pH regions was  $\geq 98\%$  *trans*-diol **203**.

An important feature of K-region arene oxides, which is not shared by the unsubstituted non-K-region oxides, is their susceptibility to nucleophilic attack and production of dihydrodiols. When there are electron-withdrawing substituents on the non-K-region arene oxides, their behavior is also similar to that of the K-region arene oxides. Later work has shown that in the study of **1** reported above, the chloride ions used in the medium were taking part, and



the reaction was going through *trans*-chlorohydrin **205**, particularly in the pH range of 5.5 to 7.2.<sup>126</sup> Use of  $\text{NaClO}_4$ , instead of  $\text{KCl}$ , simplified the picture.



Detailed study of the mechanism of solvolysis of a number of non-K-region arene oxides like **86**,<sup>90</sup> alkyl substituted benzene oxides,<sup>91</sup> **45**, **47**,<sup>88</sup> and **48**<sup>88</sup> has been carried out. They present a simple and consistent picture (Fig. 3). Below pH 6 all of them show general acid catalysis, and above pH 6 the rate remains constant with an increase in pH. The pH dependence of aromatization of **45** is described in terms of two independent reactions taking place

<sup>126</sup> D. L. Whalen, A. M. Ross, P. M. Dansette, and D. M. Jerina, *J. Am. Chem. Soc.* **99**, 5672 (1977).

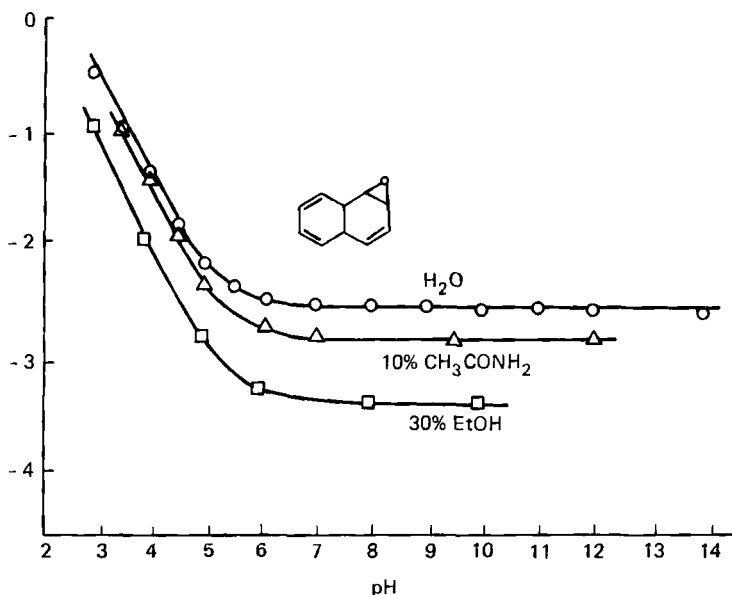


FIG. 3. The pH dependence of the aromatization of naphthalene 1,2-oxide (**45**) ( $30^{\circ}\text{C}$ ,  $\mu = 1.0$ ).

concurrently below pH 6:<sup>90</sup> (a) the spontaneous reaction involving conversion of arene oxide to a zwitterion and (b) an acid-catalyzed reaction. That the nucleophilic attack on the epoxide ring is unimportant is shown by the pH-rate profile. The Hammett–Brown plots<sup>91,127,128</sup> for the  $\text{H}_3\text{O}^+$ -catalyzed reaction as well as the spontaneous reaction of aromatization give values of  $-6.0$  and  $-5.55$ , respectively. The reaction shows a high degree of solvent isotope effect. All these studies point to the fact that the predominant reaction of non-K-region arene oxides is ring opening and subsequent NIH shift to give the eventual product, the aromatic hydroxyl compound (see Table VII<sup>129–131</sup>).

There is considerable variation in the extent of migration of the groups during the NIH shift<sup>1–5</sup>. These variations can be satisfactorily explained, as in the case of **86** as competing reactions: (a) the formation of the keto tautomer **206** and (b) the direct loss of the group from **207** by E1 elimination.<sup>90,92,129</sup>

One could conceive of the formation of two products, one with retention and other with loss of the label from **206**. The intermediate **207** is partitioned

<sup>127</sup> J. D. Richardson, T. C. Bruice, and S. M. Waraszkiewicz, and G. A. Berchtold, *J. Org. Chem.* **39**, 2088 (1974).

<sup>128</sup> D. M. Johnson and T. C. Bruice, *J. Am. Chem. Soc.* **97**, 6901 (1975).

<sup>129</sup> G. J. Kasperek, T. C. Bruice, H. Yagi, and D. M. Jerina, *J.C.S. Chem. Commun.*, 784 (1972).

<sup>130</sup> P. Y. Bruice and T. C. Bruice, *J. Am. Chem. Soc.* **98**, 2023 (1976).

<sup>131</sup> J. W. Keller and C. Heidelberger, *J. Am. Chem. Soc.* **98**, 2328 (1976).



TABLE VII  
 RATE CONSTANTS FOR THE ISOMERIZATION OF ARENE OXIDES<sup>a</sup>

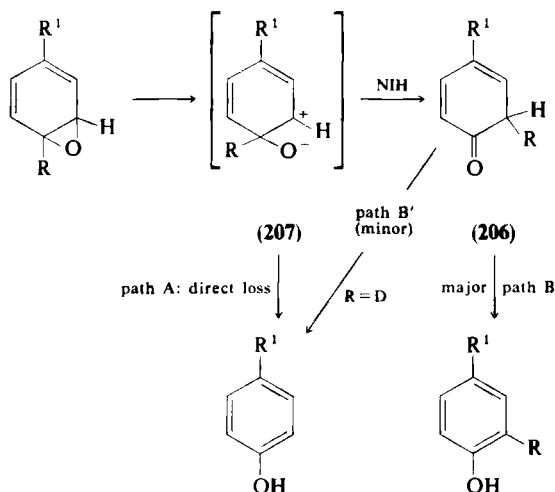
Arene oxide	$k_H$ ( $M^{-1} \text{ sec}^{-1}$ )	$k_0$ ( $\text{sec}^{-1}$ )	Reference
Benzene oxide	3.89	$2.74 \times 10^{-5}$	90, 129
	32 <sup>b</sup>	$1.4 \times 10^{-3b}$	90
	32 <sup>c</sup>	$0.89 \times 10^{-3c}$	90
	30	—	130
1-Methylbenzene oxide	105	$5.20 \times 10^{-4}$	129
3-Methylbenzene oxide	96	$9.0 \times 10^{-3}$	129
4-Methylbenzene oxide	470	$1.53 \times 10^{-2}$	129
4-Chlorobenzene oxide	0.50	$2.90 \times 10^{-5}$	
			129
1,4-Dimethylbenzene oxide	530 and 730	$4.8 \times 10^{-3}$	91
4,5-Dimethylbenzene oxide	4070	$5.28 \times 10^{-2}$	129
Indane 8,9-oxide	1410	$1.40 \times 10^{-3}$	94
Naphthalene 1,2-oxide	470 <sup>b</sup>	$3.0 \times 10^{-3b}$	90, 129
	110 <sup>d</sup>	$4.2 \times 10^{-4d}$	90
	370 <sup>c</sup>	$1.5 \times 10^{-3c}$	90
	140	—	130
Perdeuterionaphthalene 1,2-oxide	32 <sup>b</sup>	$1.33 \times 10^{-3b}$	129
	3.89	$2.74 \times 10^{-5}$	129
Phenanthrene 1,2-oxide	1000	—	130
	17	$1.15 \times 10^{-4}$	89
	—	$3.10 \times 10^{-2}$	2
Phenanthrene 3,4-oxide	2700	—	130
	38	$1.50 \times 10^{-4}$	89
	—	$5.55 \times 10^{-2}$	131
Phenanthrene 9,10-oxide	130	—	90
	30 <sup>d</sup>	—	90
	100	—	130
	4.6	—	89
	809	—	131
	—	$2.1 \times 10^{-4}$	2
Benz[ <i>a</i> ]anthracene 5,6-oxide	1480	—	131
Dibenz[ <i>a,h</i> ]anthracene 5,6-oxide	1930	—	131
3-Methylcholanthrene 11,12-oxide	99000	$3.07 \times 10^{-5}$	131

<sup>a</sup> Measured in 50% dioxane–water,  $\mu = 0.1$  in KCl at 30°C unless otherwise mentioned.

<sup>b</sup> Measured in water,  $\mu = 1.0$  in KCl at 30°C.

<sup>c</sup> Measured in 10% acetamide,  $\mu \approx 1.0$  in KCl at 30°C.

<sup>d</sup> Measured in 30% ethanol–water,  $\mu = 0.1$  in KCl at 30°C.



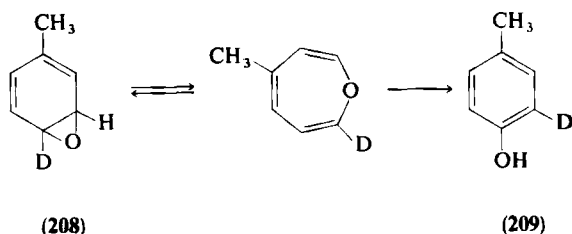
between the two paths, A and B or B'. The extent of this partitioning would depend on the nature of  $R$ . Paths A and B' lead to loss of the label, whereas path B leads to its retention. Path B' becomes available only when the labels are isotopes of hydrogen. There is evidence that conversion of **206** to the phenol is subject to a primary kinetic isotope effect.

Support comes from the work on 1-D-4-methylbenzene oxide (**208**),<sup>132</sup> which rearranged to *p*-cresol (**209**) with up to 75% retention of deuterium. Moreover, 4-D-toluene was hydroxylated to *p*-cresol, also with comparable retention. Variation in the extent of retention of deuterium has been observed, depending on the conditions (Table VIII).

TABLE VIII  
DEUTERIUM RETENTIONS AFTER ISOMERIZATION OF  
1-D-METHYLBENZENE OXIDE<sup>132</sup>

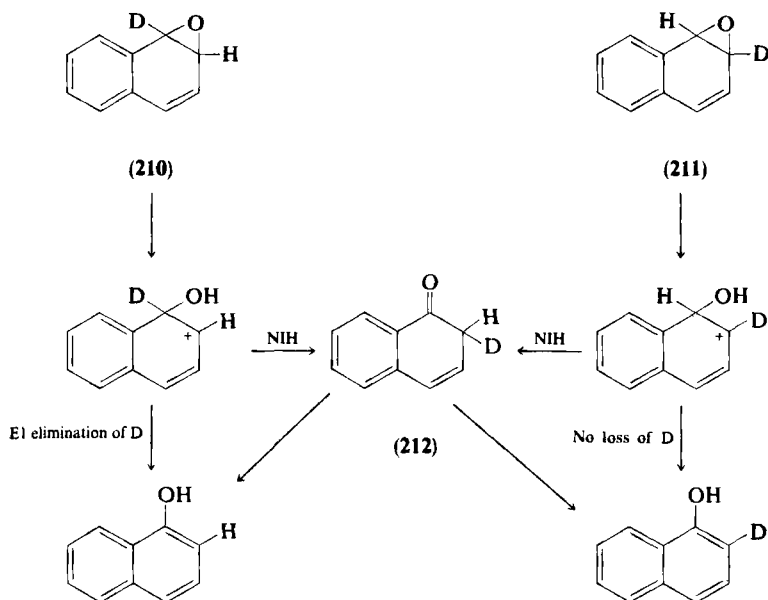
Isomerization method	Percentage retention of deuterium
0.1 N HCl	37
25°C in CCl <sub>4</sub>	58
Liver microsomes (nonenzymatic) at pH 8.0	70
Aqueous acetamide (10%)	75
Rabbit liver microsomes	56
Peroxytrifluoroacetic acid	68

<sup>132</sup> D. M. Jerina, J. W. Daly, and B. Witkop, *J. Am. Chem. Soc.* **90**, 6523 (1968).



Studies on the isomerization of 1-D- and 2-D-naphthalene 1,2-oxides (**40** and **41**, respectively) have been particularly informative<sup>133</sup> (Table IX).

With 1-D-naphthalene 1,2-oxide (**210**), the loss of deuterium depends only on the extent of the elimination of the proton, whereas with 2-D-naphthalene 1,2-oxide (**211**) the elimination reaction will not lead to any loss of D. From the table it can be seen that at low pH, elimination becomes important and competitive with retention. Above pH 7 the extent of elimination becomes insignificant



Formation of the keto tautomer of naphthol (**212**) is an important postulate in the mechanism of the NIH shift. Evidence for its formation is substantial. Whereas the retention of tritium in the neighboring positions takes place to the extent of 95%, it is only 80% in the case of deuterium. This variation clearly

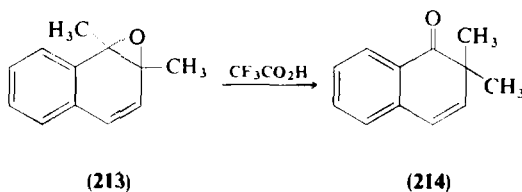
<sup>133</sup> D. R. Boyd, J. W. Daly, and D. M. Jerina, *Biochemistry* 11, 1961 (1972).

TABLE IX  
DEUTERIUM RETENTION AFTER ISOMERIZATION<sup>133</sup> OF 1-D- AND  
2-D-NAPHTHALENE 1,2-OXIDE TO 1-NAPHTHOL

Isomerization conditions	Percentage deuterium in 1-naphthol after isomerization <sup>a</sup>	
	1-D	2-D
Liver microsomes (pH 9.0 tris buffer)	75	72
Acetic acid	70	83
pH 3	59	85
pH 4	58	85
pH 5.5	71	84
pH 7.0	80	81
pH 8.5	81	80

<sup>a</sup> The oxides contained 1.00 deuterium atom. Retention figures cited are accurate to  $\pm 2\%$ .

is due to the primary isotope effect for enolization, which is much higher in the case of tritium than deuterium. Moreover, in a number of cases when the migrating group is other than hydrogen and the  $\alpha$ -position also carries a group other than hydrogen, the keto products have been isolated, e.g., 1,2-dimethylnaphthalene 1,2-oxide (**213**) gave the corresponding keto derivative **214** with trifluoroacetic acid.<sup>96,134</sup> Incidentally, it is observed that **213** is highly stable toward acids and needed strong acids like trifluoroacetic to bring about the shift.



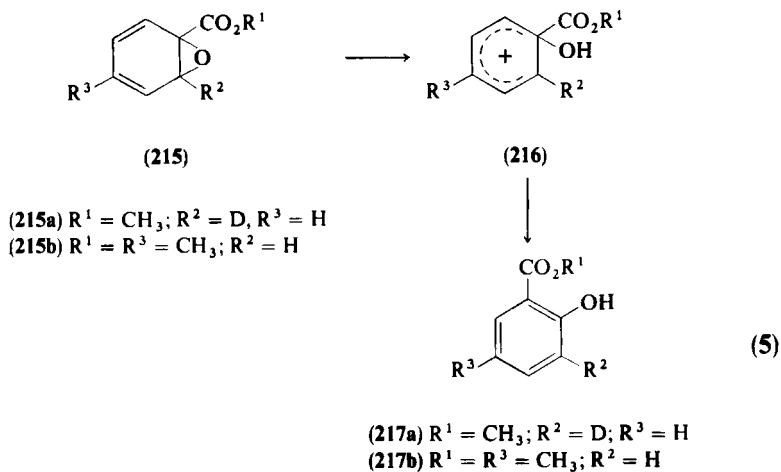
Direct evidence for the involvement of **212** was obtained by direct spectroscopic means when **45** was photolyzed at  $-196^\circ\text{C}$ . This unstable intermediate isomerized to 1-naphthol when warmed to  $-80^\circ\text{C}$ .<sup>135</sup>

Biologically, the para position of a substituted benzene derivative is the most common target for hydroxylation in the animal kingdom. By contrast, ortho hydroxylation is more common in microbial and plant metabolism. The

<sup>134</sup> N. Kaubisch, J. W. Daly, and D. M. Jerina, *Biochemistry* **11**, 3080 (1972).

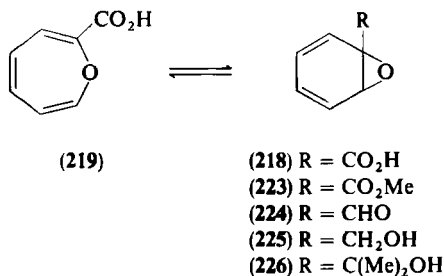
<sup>135</sup> D. M. Jerina, B. Witkop, C. McIntosh, and O. Chapman, *J. Am. Chem. Soc.* **96**, 5578 (1974).

first unequivocal evidence for the arene 1,2-oxide aromatization reaction proceeding to phenol with substituent migration was given by Boyd and Berchtold.<sup>81</sup> Studies on substituted 1-alkoxycarbonylbenzene oxide aromatization reaction indicate the mechanism shown in Eq. (5).



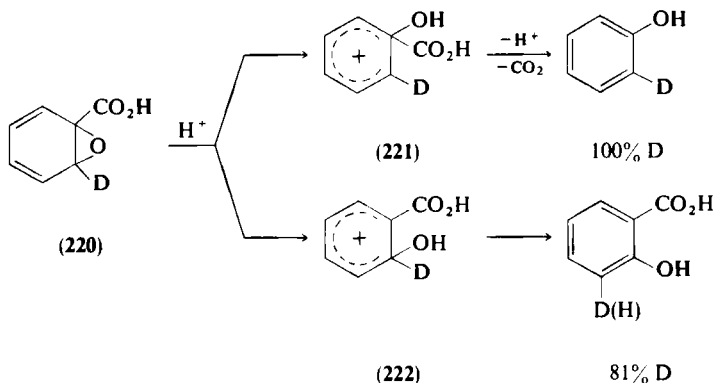
That the course of reaction for aromatization of the oxides **215** occurs exclusively via cation **216** was established from acid-catalyzed aromatization of oxides **215a** and **215b**. Rearrangement of **215a** affords **217a** with 55% retention of deuterium, and the deuterium is retained at the position ortho to the hydroxyl group. Also formation of **217b** as the sole product of aromatization of **215b** is consistent only with the pathway involving migration of the  $\text{CO}_2\text{CH}_3$  group. Thus it is clear that the acid-catalyzed rearrangement of 1-alkoxycarbonylbenzene oxide and its 2-D-2- $\text{CH}_3$ , 4- $\text{CH}_3$ , and 2- $\text{CH}_3\text{O}_2\text{C}$  derivatives occurs exclusively by an NIH shift involving migration of the  $\text{CO}_2\text{CH}_3$  group.

The 1,2-oxides of benzoic acids are also of interest as possible intermediates in the ortho hydroxylation and oxidative decarboxylation of aromatic acids. Ultraviolet studies indicate that benzene oxide **218** predominantly exists as its



oxepin valence isomer **219**. Its aromatization affords a mixture of salicylic acid and phenol, their ratio being pH dependent. Derivatives of **218** having a methyl group in the 2- or 4-position are reported to decarboxylate to *o*- and *p*-cresols on attempted isolation.

Examination of the isomerization of the deuterium-labeled **220** has led to postulation of the mechanism shown in Scheme 1. Acid **220** on aromatization



SCHEME 1

gives phenol with complete retention of deuterium and salicylic acid with 72% deuterium retention on the aromatic ring ortho to the hydroxyl group. Deuterium retentions in trifluoroacetic acid and in aqueous solutions at pH 4 (phosphate buffer) are 64 and 81%, respectively. The data are consistent with a pathway involving mainly the ring opening of the oxiranes either prior to or after protonation to afford **221** or **222** or the corresponding carboxylates, depending on the pH of the reaction medium. Carbocation **221** undergoes decarboxylation to phenol with complete retention of deuterium. Carbocation **222** undergoes migration of deuterium to an unsubstituted ortho position. After subsequent enolization, the observed deuterium retention is consistent with that expected from the operation of the isotopic effect.

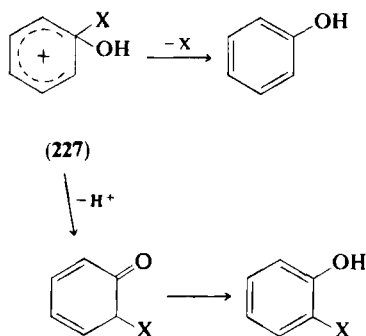
Thus phenol formation from the monocarboxylic acids described above supports the suggestion that the 1,2-oxides of aromatic carboxylic acids may be the intermediates in their biological oxidative decarboxylation reactions.

The formation of salicylic acid from **218** and the D migration and retentions observed in the conversion of **220** to salicylic acid are in agreement with the suggestion that **218** is an intermediate in the ortho hydroxylation of benzoic acid in higher plants, notwithstanding the fact that a 2,3-oxide is an equally attractive intermediate.

The aromatization pathways of 1-carboxy-, 1-methoxycarbonyl-, 1-formyl-, 1-(hydroxymethyl)-, and 1-(2-hydroxy-2-propyl)benzene oxides (**218**, **223**,

**224**, **225**, and **226**, respectively) in 1:1 aqueous THF at various pH values were examined by product analysis and D-labeling studies.<sup>82</sup> These provide examples of arene 1,2-oxide aromatization proceeding by all the possible general routes to ortho-substituted phenols and phenols with substituent loss. The extent of oxirane ring opening at C-1 versus C-2 of arene 1,2-oxides appears to be determined primarily by the electron-withdrawing or electron-donating character of the substituents, although other factors could also be involved.

Thus **223** isomerizes to methyl salicylate; the extent of  $\text{CO}_2\text{CH}_3$  migration during product formation is 70% at pH 0.1 and 83% at pH 7. Oxide **218** gives salicylic acid (40% at pH 1 and 20% at pH 7) and phenol (60% at pH 1 and 80% at pH 7), salicylic acid being formed without migration of the  $\text{CO}_2\text{H}$  group. Aromatization of **224** (pH 0.1–10) gives 88–94% phenol and 6–12% salicylaldehyde without migration of the formyl group. Isomerization of **225**, on the other hand, gives (pH 1.1–10) 8–17% phenol and 83–92% *o*-hydroxybenzyl alcohol without migration of the hydroxymethyl group. Oxide **226** on rearrangement produces 40–45% phenol and 55–60% *o*-hydroxy- $\alpha,\alpha$ -dimethylbenzyl alcohol at pH 1.1–10.



If the reaction occurs by cleavage of the oxirane ring at C-2 to afford cation **227**, migration or loss of the C-1 substituent depends on the nature of the substituent. If the substituent is a  $\text{CO}_2\text{CH}_3$  group, migration is observed. On the other hand, if the substituents are  $\text{CO}_2\text{H}$ ,  $\text{CHO}$ , or  $\text{CR}_2\text{OH}$  ( $\text{R} = \text{H}$  or  $\text{CH}_3$ ) groups, fragmentation to yield a proton and a stable, neutral molecule becomes the favored process, and substituent migration is not observed.

A number of fungi (e.g., *Aspergillus niger*) metabolize polycyclic hydrocarbons through hydroxylations and *O*-demethylation.<sup>136,137</sup> Para hydroxy-

<sup>136</sup> D. R. Boyd, R. M. Campbell, H. C. Craig, C. G. Watson, J. W. Daly, and D. M. Jerina, *J.C.S. Perkin Trans I*, 2438 (1976).

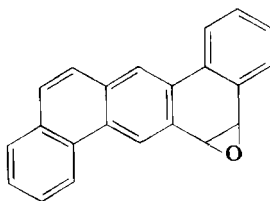
<sup>137</sup> S. M. Bocks, J. R. Lindsay-Smith, and R.O.C. Norman, *Nature (London)* **201**, 398 (1964).

lation of deuterated monosubstituted aryl rings (e.g., anisole) by fungi proceeds with migration of D (NIH shift) and involves only 3,4-oxide intermediates, as found during metabolism by plants and animals. The stereospecificity of isomerization of the intermediate arene oxide to a *p*-hydroxylated product is governed by the electronic influence of the OCH<sub>3</sub> group. For ortho hydroxylation, either 2,3- or 1,2-oxide intermediates are necessary. Low D retention on the ortho hydroxylation of phenylacetic acid and phenoxyacetic acid by *A. niger* could arise either due to involvement of a 1,2-epoxide or because of direct substitution by hydroxyl radicals. No evidence has, however, been found for an arene oxide isomerase enzyme.

### B. REACTIONS OF ARENE OXIDES WITH NUCLEOPHILES

Owing to the great biological importance of arene oxides as possible intermediates in necrosis and mutagenesis and reactive intermediates produced in the metabolism of drug molecules, a great deal of attention has been paid to understanding the reactions of nucleophiles with arene oxides. The important question is how and under what circumstances do the biological tissues react. Is the oxirane ring intact or is an electrophile formed by opening of the oxirane ring?

Keller and Heidelberger<sup>131</sup> reported the kinetics of solvolysis of **1**, **30**, **38**, and benz[*a,h*]anthracene 5,6-oxide (**228**). These studies were carried out mostly in the pH < 7 region where nucleophilic addition ordinarily does not take place with either K-region or non-K-region epoxides. These authors found evidence for the formation of a carbonium ion and consequently were led to believe that the cell macromolecules react with arene oxides through a carbonium ion-trapping mechanism and not by a direct nucleophilic displacement on the oxides.



(228)

Detailed studies by Bruce, Jerina, and co-workers, referred to earlier, showed that three factors determine whether nucleophilic reaction of tissue materials with arene oxides occur directly. They are (a) the structure of the



arene oxide, whether it is a K-region or non-K-region arene oxide (the non-K-region arene oxides with electron-withdrawing substituents also behave as K-region arene oxides in this particular situation); (b) the pH of the medium, whether it is 7 and above, and (c) the nature of the nucleophile, whether it is soft (polarizable), like  $N_3^-$  or  $RS^-$ , or hard, like nonpolarizable nitrogen and oxygen bases.

Detailed study of the rearrangement of **86**, **45**,<sup>90</sup> **47**,<sup>130</sup> **181**,<sup>91</sup> and **162**<sup>95</sup> has been carried out. From the pH-rate profiles it was found that increasing the  $OH^-$  concentration from  $10^5$ - to  $10^7$ - fold did not bring about any increase in the rate of disappearance of the oxide, showing that aromatization is the dominant reaction.

In non-K-region epoxides like **86**, second-order nucleophilic addition and water-catalyzed aromatization compete. Nitrogen and oxygen nucleophiles are not able to compete, whereas polarizable nucleophiles do. The factor most important is apparently the polarizability of the nucleophile rather than its basicity. The basicity of the thiolate species has little influence on the rate of reaction of **86** (Bronsted  $\beta$ -value = 0.2).<sup>138,139</sup>

Comparison of the reactivities of benzene oxides, naphthalene oxides, phenanthrene oxides, and arene oxides derived from benzo[*a*]pyrene and 7,12-dimethylbenz[*a*]anthracene with hepatic glutathione *S*-epoxide transferase showed that benzene oxides without electron-withdrawing groups are poor substrates as also are polycyclic arene oxides. Only naphthalene oxide was a good substrate.

The K-region oxides undergo nucleophilic addition with  $OH^-$ ,  $CO_3^{2-}$ , water, amines, and mercaptides.<sup>88,140</sup> The second-order rate constants for the reactions of  $OH^-$ , water, and primary and secondary amines with **1** at 30°C and with ethylene oxide at 25°C<sup>141</sup> can be simply related by Eq. (6),<sup>2</sup> which shows that the sensitivity of the two oxides to the nature of the nucleophile is similar and that the arene oxide is more reactive.

$$\log k_n[\mathbf{1}] = 1.3 \log k_n[\text{ethylene oxide}] + 1.7 \quad (6)$$

$$\log k_n[\mathbf{1}] = 0.35 \log k_n[\text{ethylene oxide}] + 0.96 \quad (7)$$

Equation 7 applies for thiolate anion addition. Ethylene oxide is nearly three times more sensitive than **1** to the nucleophilicity of the thiol. The second-order rate constants for the reactions of 2-mercaptoethanol with **1**, **47**, and **48** are 3.32, 1.58, and 2.04  $M^{-1} \text{ sec}^{-1}$ , respectively. This shows that **1** is only slightly more reactive and that the K-region does not necessarily make the

<sup>138</sup> D. M. E. Reuben and T. C. Bruice, *J.C.S. Chem. Commun.*, 113 (1974).

<sup>139</sup> D. M. E. Reuben and T. C. Bruice, *J. Am. Chem. Soc.* **98**, 114 (1976).

<sup>140</sup> P. Y. Bruice, T. C. Bruice, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.* **98**, 2973 (1976).

<sup>141</sup> P. O. I. Virtanens and R. Korhonen, *Acta Chem. Scand.* **27**, 2650 (1973).

epoxide a better alkylating agent, a significant finding in terms of understanding the molecular basis of carcinogenesis. The most important factor, therefore, that determines whether the arene oxide behaves as an alkylating agent is its capacity to survive the spontaneous or solvent-catalyzed aromatization reaction. A comparison of the rates for spontaneous decomposition of epoxides of phenanthrene illustrates this point. The values of  $k_1$  ( $H_2O$ ) are  $3.10 \times 10^{-2}$ ,  $5.55 \times 10^{-2}$ , and  $2.1 \times 10^{-4} \text{ sec}^{-1}$  for **47**, **48**, and **1**, respectively. The lifetime of the 9,10-oxide is greater than that of its isomers by almost 100 times between pH 5 and 7, and 1000 times between pH 8.5 and 11.5.

To quantify the partitioning of the decomposition of arene oxides to the two competing pathways of nucleophilic attack or spontaneous/solvent-mediated ring opening, Bruice and Bruice developed a nucleophilic susceptibility index.<sup>2</sup> This is defined as the relative rate of attack by 2-mercaptoethanol on the oxirane ring divided by the relative rate of water-catalyzed epoxide ring opening. Values of the nucleophilic susceptibility indices for a number of arene oxides are given in Table X;<sup>142,143</sup> **1** closely resembles ethylene oxide, an effective alkylating agent.

TABLE X  
RELATIVE RATES OF SPONTANEOUS RING OPENING (A) AND THIOLATE  
ANION NUCLEOPHILIC ATTACK (B)<sup>a</sup>

Compound	A <sup>b</sup>	B <sup>c</sup>	B/A <sup>d</sup>
Ethylene oxide	1 <sup>e</sup>	1 <sup>f</sup>	1
Benzene oxide	1900 <sup>g</sup>	4 <sup>h</sup>	0.002
Naphthalene 1,2-oxide	5000 <sup>g</sup>	41 <sup>i</sup>	0.008
Phenanthrene 1,2-oxide	50000 <sup>g</sup>	39 <sup>j</sup>	0.0008
Phenanthrene 3,4-oxide	90000 <sup>g</sup>	50 <sup>i</sup>	0.0006
Phenanthrene 9,10-oxide	40	82 <sup>i</sup>	2
<i>t</i> -Butoxycarbonylbenzene oxide	250 <sup>j</sup>	7200	30
4-Carboxybenzene oxide	600	11	0.02

<sup>a</sup> According to ref. 142.

<sup>b</sup> Ethylene oxide measured at 25°C, all others at 30°C.

<sup>c</sup> Attack on ethylene oxide measured at 20°C, all others at 30°C.

<sup>d</sup> Nucleophilic susceptibility index.

<sup>e</sup> According to ref. 141.

<sup>f</sup> According to ref. 143.

<sup>g</sup> According to ref. 88.

<sup>h</sup> According to ref. 139.

<sup>i</sup> According to ref. 140.

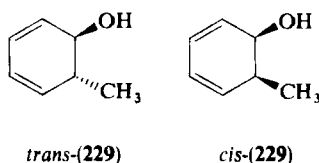
<sup>j</sup> According to ref. 128.

<sup>142</sup> P. Y. Bruice, S. C. Wilson, and T. C. Bruice, *Biochemistry* **17**, 1662 (1978).

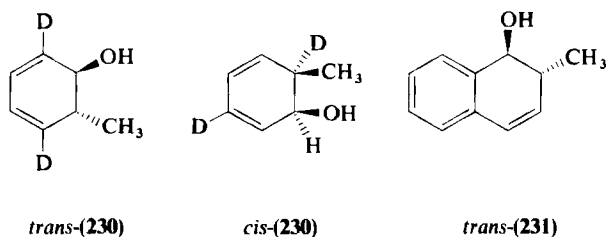
<sup>143</sup> J. P. Danehy and C. J. Noel, *J. Am. Chem. Soc.* **82**, 2511 (1960).

### 1. Reaction with Organometallic Reagents

Vogel and Gunther<sup>8</sup> have reported that **86** reacts with methyllithium to give a mixture of *cis*- and *trans*-6-methylcyclohexane-2,4-dienols (**229**) in which the *cis*:*trans* ratio is higher than 9. Formation of the *cis* isomer as a major product in the reaction suggests that the reaction predominantly occurs through a *cis* 1,6-addition. Repetition of the reaction by Jeffrey *et al.*<sup>144</sup> yielded only *cis*-(**229**) in 67% yield. The reaction with dimethylmagnesium yielded a 37:63 mixture of *cis*- and *trans*-(**229**) in 26% yield.



Information on the site of attack by the organometallic reagents on **86** was obtained, using the reaction of benzene oxide-oxepin-3,6-D<sub>2</sub>. Methyllithium produced *cis*-(**230**) by exclusive 1,6-addition. Analysis of the *cis* alcohol obtained from the reaction of dimethylmagnesium shows it to be *cis*-(**230**) resulting from substitution at the 3-carbon atom, whereas *trans*-(**230**) is formed directly by *trans* 1,2-addition. Methyllithium, by contrast, leads only to 1,2-*trans* product **231** with **45**.



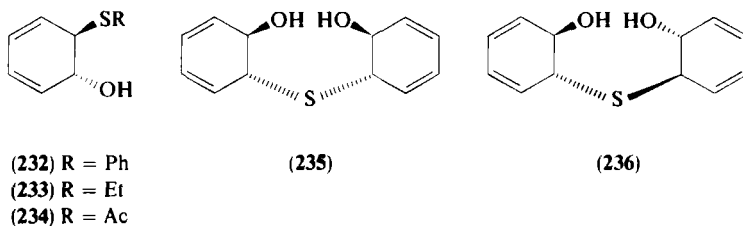
### 2. Reactions with Sulfur Nucleophiles

Addition of sodium thiophenoxide to **86** in aqueous medium furnishes *trans*-6-phenylthiocyclohexa-2,4-dienol (**232**) in 64% yield. The reaction with 1,2,3,4,5-D<sub>5</sub>-(**86**) established that the addition of PhS<sup>-</sup> proceeds by direct *trans* 1,2 ring opening. Similarly, the addition of thioethanol and thioacetates to **86** proceeds by 1,2 ring opening and *trans*-(**234**) is formed.<sup>144</sup> Reaction of **86**

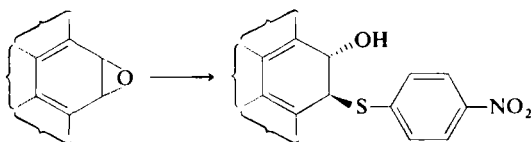
<sup>144</sup> A. M. Jeffrey, H. J. C. Yeh, D. M. Jerina, R. M. DeMarinis, C. H. Foster, D. E. Piccola, and G. A. Berchtold, *J. Am. Chem. Soc.* **96**, 6929 (1974).

and **45** with thiocyanate ion produces benzene and naphthalene, respectively, with only traces of thionaphthols.<sup>145</sup>

Reaction of **86** with sulfide ion produces both meso (**235**) and racemic (**236**) diastereomers of bis(6-*trans*-1-hydroxycyclohexa-2,4-dienyl) sulfide.



Agarwal *et al.*<sup>146</sup> examined the reactions of epoxides with *p*-nitrothiophenol and found that the mono- and di-epoxides undergo facile nucleophilic opening by *p*-nitrothiophenol to yield the 1,2-adducts cleanly in good yield. They have advocated this reaction as a suitable method for trapping atmospheric epoxide contaminants. These adducts show an intense protonated molecular ion in chemical ionization mass spectra. Their detection and characterization by the technique of single-ion monitoring has been suggested.



A detailed study of the reaction of *t*-butyl mercaptide anion with K-region epoxides, derived from carcinogenic and related polycyclic hydrocarbons, was carried out in aqueous dioxane and in THF.<sup>147</sup> In the former solvent system, 1,2-*trans* stereospecific addition took place, whereas addition-dehydration was observed in THF.

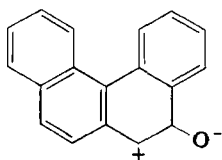
In cases where the oxirane ring is unsymmetrically substituted, the product structure can be predicted on the basis of attack at the most electrophilic center. This center has the lowest Dewar reactivity number ( $N_1$ ) as predicted by MO calculations. The following example is illustrative. Benzo[*c*]phenanthrene 5,6-oxide (**31**) could give rise to two different zwitterions (**237** and **238**). The former has a Dewar reactivity number 1.79 and the

<sup>145</sup> R. M. DeMorinis and G. A. Berchtold, *J. Am. Chem. Soc.* **91**, 6525 (1969).

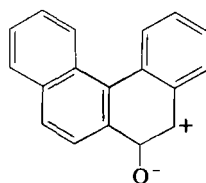
<sup>146</sup> S. C. Agarwal, L. Benjamin, D. Van, J. J. Solomon, and S. A. Kline, *Environ. Sci. Technol.* **14**, 1249 (1980).

<sup>147</sup> F. A. Beland and R. G. Harvey, *J. Am. Chem. Soc.* **98**, 4963 (1976).

latter has 1.86. The experimental results showed that the product is derived from the reaction of **237**.

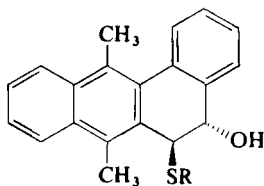


(237)

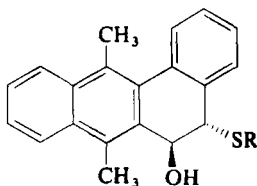


(238)

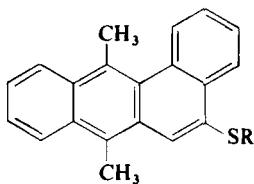
However, regiospecificity is not observed in all cases. Steric hindrance has to be considered. Reaction of **30** gave a 4:1 mixture of **239** and **240**. Dehydration with *p*-toluenesulfonic acid surprisingly gave only **241**. The formation of **241** from **239** or **240** is attributed to the migration of the thioalkyl group through a cyclic sulfonium intermediate (**242**).<sup>147a</sup>



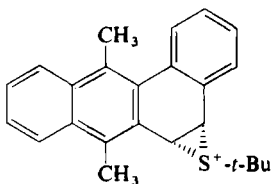
(239)



(240)



(241)

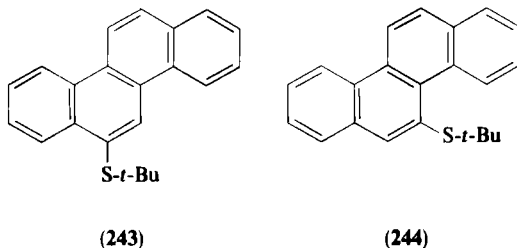


(242)

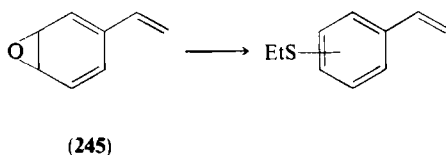
Compound **5**, for which the  $N_t$  values differ by only 0.23, affords a 75:25 ratio of the isomers **243**:**244** according to prediction. But in the case of **31**, for which the difference for the two positions is only 0.13, the predicted isomer was formed exclusively. This has been explained on the basis of greater steric crowding at the 5 position. The hydrogen atoms at the 4 and 5 positions tend

<sup>147a</sup> A. M. Jeffrey and D. M. Jerina, *J. Am. Chem. Soc.* **97**, 4427 (1975).

to force the oxirane protons out of the plane of the polycyclic ring and thereby hamper the approach of the nucleophile.

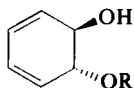


Very recently, the reaction of styrene 3,4-epoxide (**245**) with ethyl mercaptan has been reported.<sup>148</sup> A mixture of 2-, 3-, and 4-ethylthiostyrenes is formed in the ratio of 1:9:7 along with small amounts (18%) of 4-vinylphenol. These results can be explained as nucleophilic attack on the intact arene oxide and the reaction of the zwitterion formed by the spontaneous reaction.



### 3. Reactions with Oxygen Nucleophiles

The reactivity of **86** and **45** with alkoxides is very low. Reaction of **86** with a trace of methoxide in methanol yields 78% of *trans*-(**246**) after 69 days. Attempts to add ethoxide to **86** lead mainly to phenol. Storage of **86** in ethanol for about 2 months at room temperature gives only a small amount of **247**.



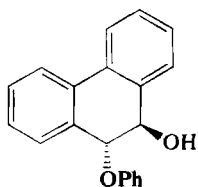
(**246**) R = CH<sub>3</sub>  
 (**247**) R = C<sub>2</sub>H<sub>5</sub>

1,2-Trans addition of methoxide ion to K-region as well as non-K-region arene oxides is achieved under mild conditions (25°C in ether) in good yield, using a Woelm alumina catalyst.<sup>149</sup> This reaction is discussed in Section V,B,4.

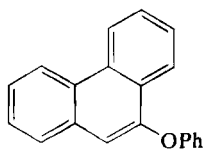
<sup>148</sup> T. Watabe, A. Hiratsuka, T. Sone, and T. Ishihama, *J.C.S. Chem. Commun.*, 585 (1983).

<sup>149</sup> G. H. Posner and D. Z. Rogers, *J. Am. Chem. Soc.* **99**, 8214 (1977).

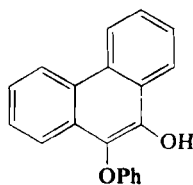
With K-region oxides, sodium salts of phenol or cresols also produce addition products. Thus heating a mixture of **1** and sodium phenoxide in dimethylformamide at 100°C under a nitrogen atmosphere produced 9,10-dihydro-*trans*-9-hydroxy-10-phenoxyphenanthrene (**248**, 19%), 9-phenoxyphenanthrene (**249**, 68%), and traces of 9-phenanthrol and phenanthrene-9,10-quinone. When the reaction was carried in the presence of air, a significant amount of 9-hydroxy-10-phenoxyphenanthrene (**250**) was formed instead of **248** and **249**.<sup>150</sup>



(248)

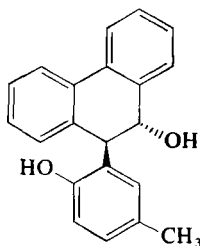


(249)

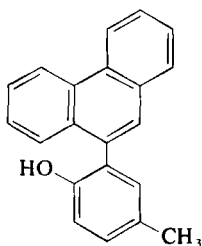


(250)

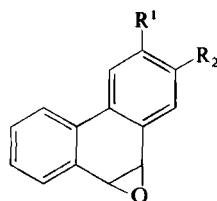
Similar results have been obtained in the reactions of **1** and sodium salts of *p*-cresol and  $\alpha$ - and  $\beta$ -naphthols. Under  $S_N2$  conditions (DMF or DMSO solvent), the alkylation of sodium cresolate occurs exclusively at the oxygen atom. The addition of a protic solvent causes C-alkylation, though the yields of C-alkylated products are low. Thus in acetone-water or dioxane-water, the yield of C-alkylated products **251** and **252** increases only up to 2%. C-Alkylation has also been observed in the reactions catalyzed by trifluoroacetic acid or boron trifluoride etherate at room temperature. The observed C-alkylation in protic media may be a reflection of a mechanism that involves a protonated epoxide or a more polarized transition state than in an  $S_N2$  pathway.



(251)



(252)

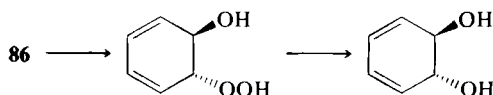
(253)  $R^1 = OCH_3, R^2 = H$ (254)  $R^1 = H, R^2 = OCH_3$ 

<sup>150</sup> T. Okamoto, K. Shudo, and S. Nagata, *Chem. Pharm. Bull.* **23**, 687 (1975).

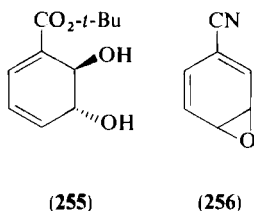
A study carried out with various K-region arene oxides shows that the reactivity order of epoxides with sodium cresolate in DMSO is **29** > **28** > **1**, **253** > **4** > **254**. The poor regioselectivity observed in the reactions of **28** and **29** with the cresolate is attributed to the insensitivity of the reaction to electronic influences as well as by the inherent absence of the electronic effects on the condensed benzo ring.<sup>24</sup>

Attempts to add  $\text{OH}^-$  and the more nucleophilic<sup>151</sup>  $\text{HOO}^-$  to **86** in aqueous solution were unsuccessful. However, with the more stable *t*-butylhydroperoxide in *t*-butanol containing potassium *t*-butoxide, the only detectable products were phenols and diphenyl ether. Presumably the phenolate ion formed *in situ* from **86** was able to compete successfully with the alkoxide.

The reaction of **86** with a large excess of  $\text{H}_2\text{O}_2$  and an aqueous base, followed by borohydride reduction, gives the *trans*-diol in 30% yield.



Reaction of 4-*t*-butoxycarbonylbenzene oxide (**111**,  $\text{R} = t\text{-Bu}$ ) with lithium hydroxide in aqueous dioxane yielded *t*-butyl *trans*-2,3-dihydroxy-2,3-dihydrobenzoate (**255**).<sup>152</sup> In an aqueous solution, the compound undergoes both  $\text{H}_3\text{O}^+$ - and water-catalyzed aromatization as well as a  $\text{HO}^-$ -catalyzed reaction at higher pH ranges. With a more electron-deficient 4-cyanobenzene oxide (**256**) the kinetics of the base-catalyzed hydrolysis show a first-order dependence on  $[\text{HO}^-]$  above pH 9.<sup>2</sup>



#### 4. Reactions with Nitrogen Nucleophiles

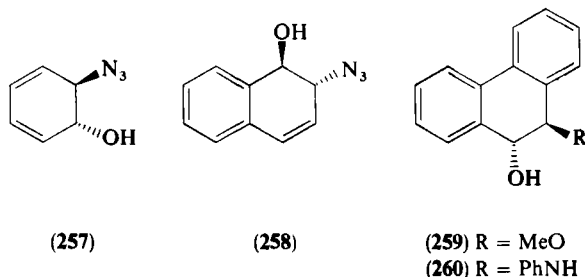
Nitrogen nucleophiles, unless polarizable, are unreactive toward **86**. Thus ammonia and  $\text{NH}_2^-$  do not add to **86**, whereas  $\text{N}_3^-$  reacts readily.<sup>145</sup>

<sup>151</sup> J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.* **84**, 16 (1962).

<sup>152</sup> R. M. DeMarinis, C. N. Filer, S. M. Waraszkiewicz, and G. A. Berchtold, *J. Am. Chem. Soc.* **96**, 1193 (1974).



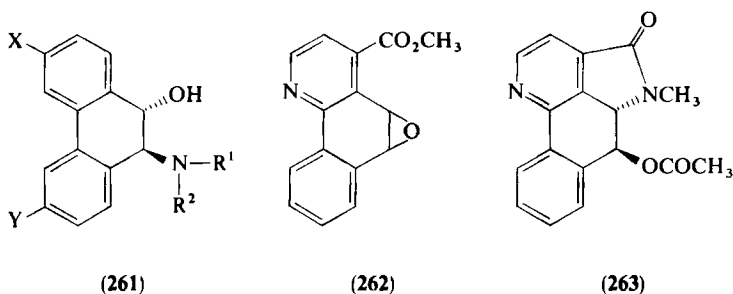
The non-K-region oxide **45** is 250 times more susceptible to spontaneous epoxide ring opening and aromatization than is the K-region oxide **1**. Reaction of **45** with sodium methoxide has been reported.<sup>150</sup> Posner and Rogers<sup>149</sup> have developed a method for the reaction of nonpolarizable oxygen and nitrogen nucleophiles with arene oxides on Woelm-200 basic alumina under mild conditions (25°C, ether solvent). Under these conditions K- and non-K-region epoxides give 1,2-trans ring-opened products. Under these conditions nucleophilic incorporation competes successfully with aromatization. Thus **1** under these conditions reacts with methanol to give the trans adduct **259** (88%) and 9-phenanthrol (11%), whereas with aniline it furnishes the trans adduct **260** (79%) and 9-phenanthrol (~10%).



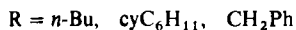
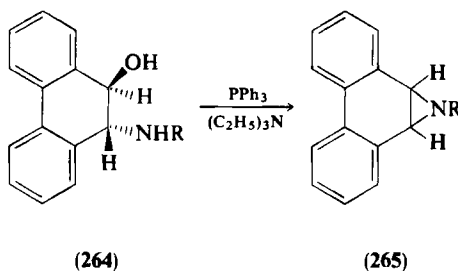
45

MeO)	34%	44%	0%
<i>n</i> -BuNH)	30%	25%	25%
PhNH)	24%	31%	11%

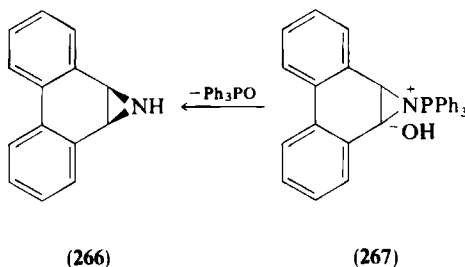
<sup>155</sup> J. I. Levin and S. M. Weinreb, *J. Am. Chem. Soc.*, **105**, 1397 (1982).



Oxide **1**, when treated with primary amines like *n*-butyl-, cyclohexyl-, or benzylamine, gives *trans*-9,10-amino alcohols (**264**). These amino alcohols have been utilized for the preparation of aziridine **265** by treatment with trialkyl- or triarylphosphines.<sup>156</sup>



A stereospecific synthesis of aziridine **266** has been reported by Ittah *et al.* from arene oxide **1** by treatment with sodium azide, followed by triphenylphosphine reaction. The reaction proceeds via a phosphonium hydroxide intermediate (**267**).<sup>157</sup>



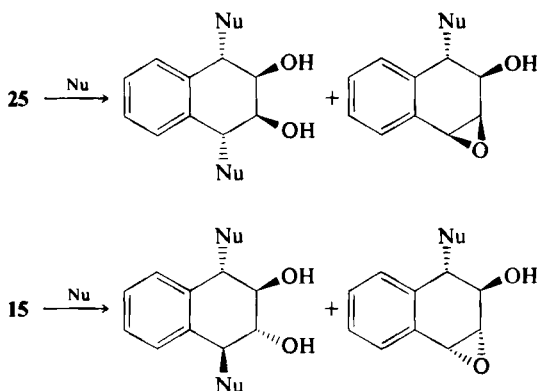
<sup>156</sup> Y. Ittah, I. Shahak, and J. Blum, *J. Org. Chem.* **43**, 397 (1978).

<sup>157</sup> Y. Ittah, Y. Sasson, I. Shahak, S. Tsaroom, and J. Blum, *J. Org. Chem.* **43**, 4271 (1978).

Based on this sequence, Blum *et al.*<sup>158</sup> have reported a general synthesis of unsubstituted K-region arene imines from the corresponding arene oxides. K-Imines of benz[*a*]anthracene, 7-methylbenz[*a*]anthracene, dibenz[*a,h*]anthracene, and benzo[*a*]pyrene have been prepared. Azido alcohol formation from these oxides is generally nonregiospecific and both possible regioisomers of the azido alcohols are formed in different proportions.

Oxides **28** and **29** react with nucleophiles like *p*-toluidine, although the reactivities of epoxides **1**, **4**, **28**, and **29** differ by a factor of less than three. It is interesting that **253** is most stable toward the attack of *p*-toluidine, showing that the carbocation-stabilizing group does not necessarily facilitate the reaction with nucleophiles.

The reactivity, site of attack, and stereochemistry of the reactions of a variety of nucleophiles (oxygen, sulfur, nitrogen, organometallic) with *anti*- and *syn*-naphthalene 1,2:3,4-dioxides have been studied recently.<sup>159</sup> In most cases, di- or tetrasubstituted tetrahydronaphthalene products arising from attack at C-1 and C-4 positions in the *anti* mode are produced. These isomeric diepoxides are excellent intermediates for the preparation of a number of difficultly accessible 1,4-disubstituted naphthalene derivatives.

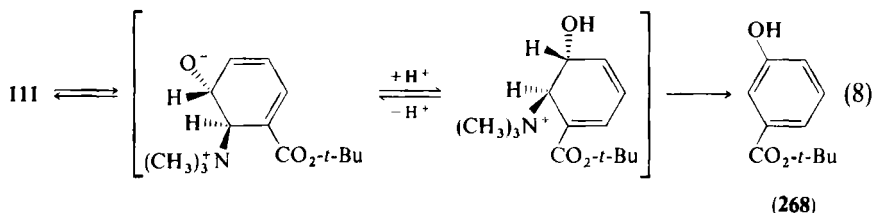


Interestingly, aromatization can also take place with nucleophilic catalysis. Thus 4-*t*-butoxycarbonylbenzene oxide (**111**, R = *t*-Bu) undergoes aromatization to *t*-butyl *m*-hydroxybenzoate (**268**) in the presence of trimethylamine. The mechanism of this reaction has been studied in considerable detail and is described as in Eq. (8).<sup>118</sup>

Soft and polarizable nucleophiles, e.g., azide, thiol anions, and phenoxides, add readily to arene oxides, whereas harder anions like carbanions and

<sup>158</sup> J. Blum, I. Yona, S. Tsaroom, and Y. Sasson, *J. Org. Chem.* **44**, 4178 (1979).

<sup>159</sup> S. Tsang, G. W. Griffin, M. G. Horning, and W. G. Stillwell, *J. Org. Chem.* **47**, 5339 (1982).

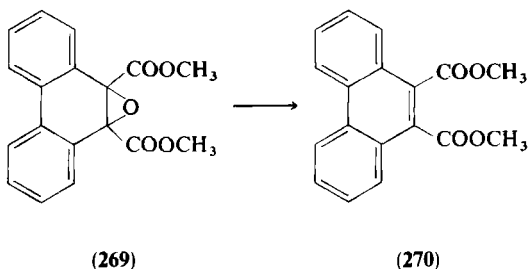


$^-OOH$  must be strongly nucleophilic in order to react. Alcohols add only with difficulty, and ammonia and  $NH_2^-$  are unreactive. The high stereospecificity for the nucleophilic addition reaction in aqueous media is indicative more of nucleophilic opening rather than of trapping of carbonium ions.

### C. MISCELLANEOUS REACTIONS

#### 1. Deoxygenation of Arene Oxides

Oxygen can be transferred from the arene oxides to nitrogen-, sulfur-, or phosphorus-containing substrates like pyridine, thiourea, *N*-methylbenzothiazol-2-thione, thioacetamide, thiosemicarbazide, thiols, thioethers, triphenylphosphine,<sup>21,160,161</sup> etc. Parent hydrocarbons are formed as products.<sup>162</sup> Thus the dimethoxycarbonyl oxide **269** on heating with pyridine produces 9,10-dimethoxycarbonylphenanthrene (**270**). The reaction of **1** or its



9,10-dimethyl derivative **2** on treatment with thiourea, 1-methylbenzothiazol-2-thione, thioacetamide, or thiosemicarbazide at 25°C in benzene or methanol furnishes the corresponding parent hydrocarbon **271**. Similarly, **4** produces pyrene.

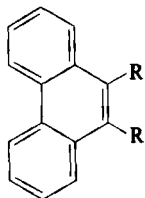
Also, **67** can be converted to the hydrocarbon **272** on treatment with pyridine, thiols, thioethers, or thiourea. These reactions can have significance

<sup>160</sup> G. Wittig and W. Haag, *Chem. Ber.* **88**, 1654 (1955).

<sup>161</sup> T. Mukaiyama, I. Kuwajima, and K. Ohno, *Bull. Chem. Soc. Jpn.* **38**, 1954 (1965).

<sup>162</sup> G. W. Griffin, K. Ishikawa, and S. K. Satra, *J. Heterocycl. Chem.* **13**, 1369 (1976).

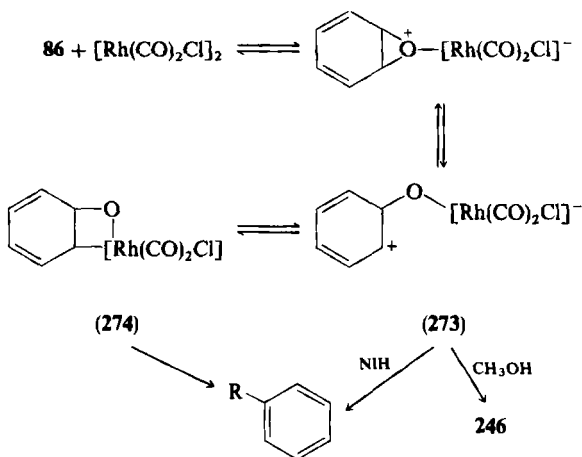
in terms of biological enzymic deoxygenation and for detoxification of arene oxides.



(271) R = H, CH<sub>3</sub>

(272) R = CN

Arene oxides when treated with triphenylphosphine also undergo deoxygenation to produce the corresponding parent aromatic hydrocarbons.<sup>8</sup> The deoxygenation, accompanied by ring cleavage, is also brought about by bis(chlorodicarbonylrhodium) catalysis. Thus **86** in deuteriochloroform at room temperature for 1 min gives a 1:1 mixture of benzene and phenol in quantitative yields.<sup>163</sup> The reaction involves Lewis acid catalysis to give intermediate **274**. Cyclization of **273** to a rhodaoxacyclobutane **274**, followed by fragmentation, produces benzene.



The deoxygenation of arene oxides have also been achieved by using chromium carbonyl complexes. The aromatic hydrocarbons produced are partially converted to chromium complexes. Formation of **246** in methanol suggests Rh-catalyzed solvolysis, resulting in nucleophilic addition of meth-

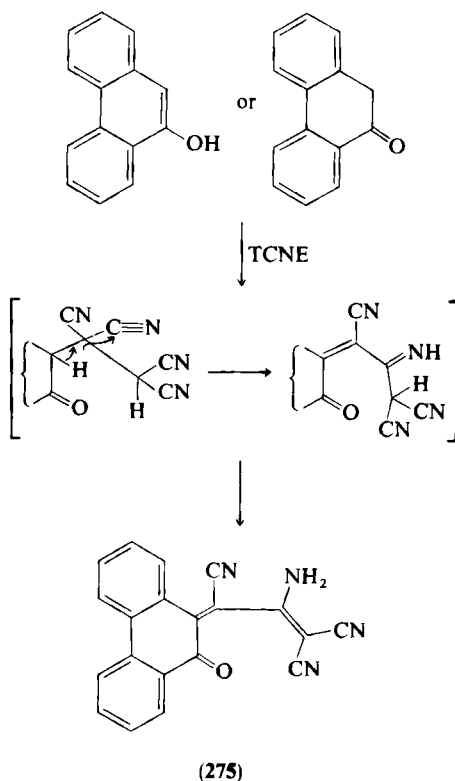
<sup>163</sup> R. W. Ashworth and G. A. Berchtold, *Tetrahedron Lett.*, 343 (1977).

anol to **273**. Arene oxides, which cannot give phenolic products without prior oxygen walk or rearrangement of the carbocyclic skeleton, undergo quantitative deoxygenation, e.g., **162** with  $[\text{Rh}(\text{CO})_2\text{Cl}]_2$  gives indane quantitatively in 10 min.

The deoxygenation of **86** to benzene can also be accomplished with lithium aluminum hydride. Conversion of **157** to the parent aromatic hydrocarbon has been brought about with hydrogen and platinum at  $0^\circ\text{C}$ .

## 2. Reaction of Phenanthrene 9,10-Oxide with TCNE

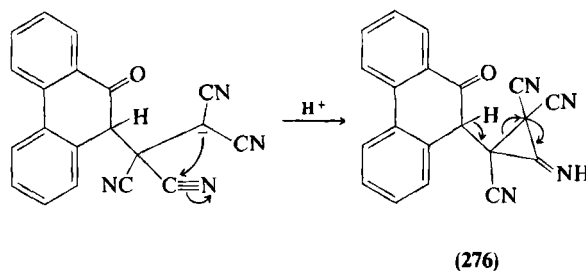
Oxide **1** reacts with tetracyanoethylene (TCNE) to give the 1:1 adduct **275**. Its structure was determined by X-ray crystallography.<sup>164</sup> The reaction is believed to proceed through the prior isomerization of the oxide to phenanthrone, followed by its reaction with TCNE as shown in Scheme 2. The



SCHEME 2

<sup>164</sup> T. Okamoto, K. Shudo, T. Ohta, A. Itai, and Y. Iitaka, *Chem. Pharm. Bull.* **26**, 334 (1978).

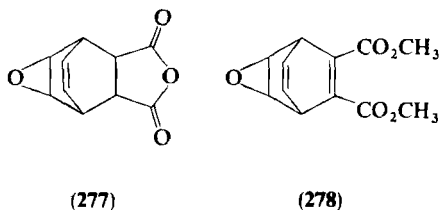
alternate possibility of the reaction proceeding through a three-membered cyclic intermediate (**276**, Scheme 3) cannot be excluded.



SCHEME 3

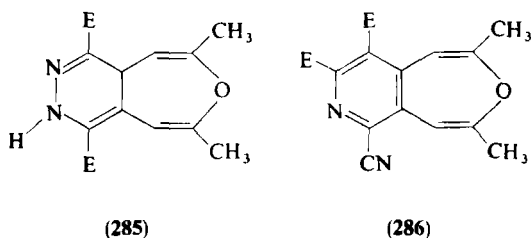
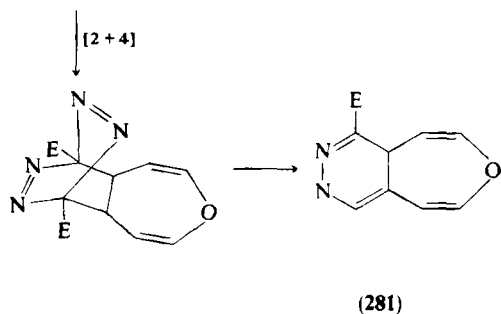
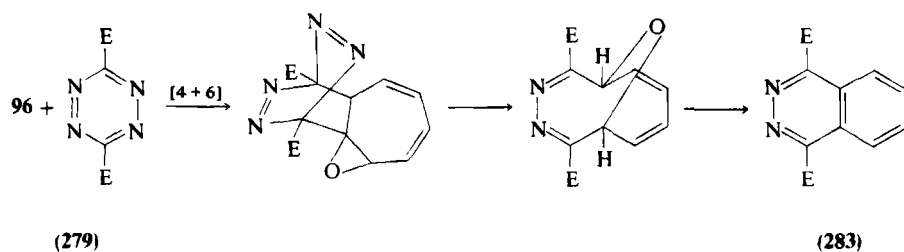
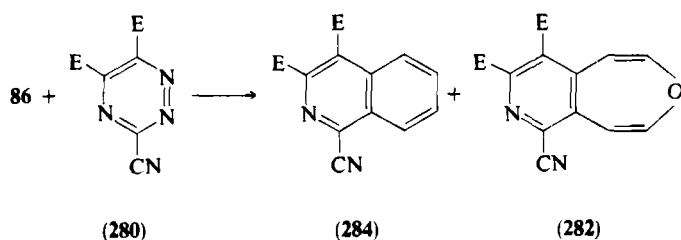
### 3. Cycloaddition Reactions

Non-K-region arene oxides react with reactive dienophiles like maleic anhydride, dimethyl acetylenedicarboxylate to give [4 + 2] Diels–Alder adducts in good yield under mild conditions.<sup>8</sup> Thus **86** reacts with maleic anhydride at 20°C within a few minutes to produce adduct **277** in quantitative yield whereas with dimethyl acetylenedicarboxylate it gives **278** in a few days at 20°C.



Arene oxide–oxepin systems have also been reported to undergo [2 + 4] or [4 + 6] pericyclic cycloaddition reactions with heterocyclic dienes like the tetrazine **279** and the triazine **280**.<sup>165</sup> Thus **86** ⇌ **96** reacts with **279** and **280** to yield the dihydrooxepino [4,5-*d*]pyridazine **281** and the oxepino[4,5-*c*]pyridine **282**, respectively, via a [2 + 4] cycloaddition as well as the phthalazine **283** and isoquinoline **284**, respectively, probably via a [6 + 4] cycloaddition reaction. However, **157** gives only **285** and **286** arising from a [2 + 4] cycloaddition reaction.

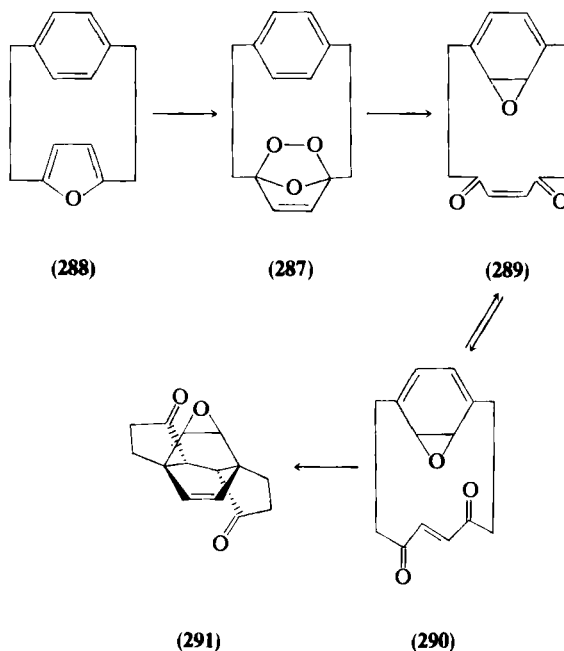
<sup>165</sup> R. Dhar, W. Huhnemann, T. Kampchen, W. Overhue, and G. Seitz, *Chem. Ber.* **116**, 97 (1983).



The ozonide **287** resulting from a singlet oxygen reaction with **288** in methanol is converted to **289** by transannular epoxidation of the benzene ring. This oxide undergoes cis-trans isomerization to **290**, and subsequent intramolecular Diels-Alder addition finally yields the novel product **291**.<sup>166</sup>

<sup>166</sup> H. H. Wasserman, A. R. Doumaux, and R. E. Davis, *J. Am. Chem. Soc.* **88**, 4517 (1966).





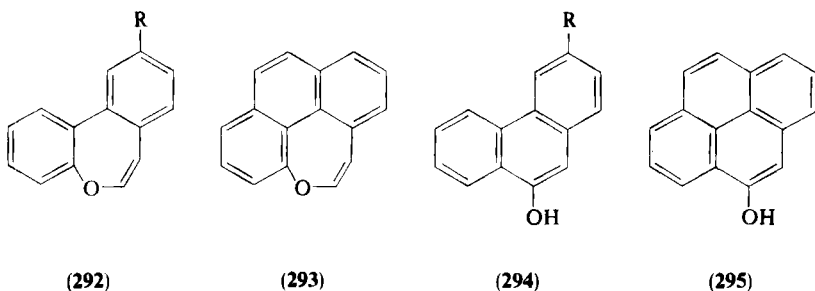
#### 4. Photochemical Reactions

Photochemical rearrangement of **1**, **4**, and **64** has been examined in dichloromethane by steady irradiation and nanosecond transient spectroscopy. The ring enlargement of **1** to **292** and **4** to **293**, respectively, has been postulated to occur via the singlet excited state. Phenolic derivatives **294** and **295** are formed from **1** and **4**, respectively, via their triplet state. Product sensitization is proposed for the conversion of **1** and **4** to **294** and **295**, respectively.<sup>167</sup> Van Duuren *et al.* have found that on UV irradiation (254 nm) in methylene chloride, **4** rearranges to oxepin **293**, 4-hydroxypyrene, pyrene, and other unidentified products.<sup>168</sup>

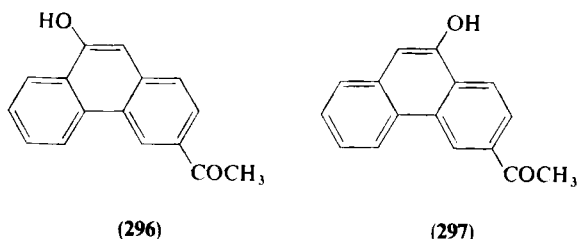
The products formed upon direct irradiation of **1** include 9-phenanthrol and fluorene. The former is believed to be formed in a triplet process. This is supported by the capacity to quench phenanthrol formation with *trans*-1,3-pentadiene and to circumvent the rearrangement to **292** (R = H) by utilization of sensitizers such as benzophenone or triphenylene. In an attempt to confirm that the chemically significant excited state in the conversion of **1** to **292**

<sup>167</sup> M. Itoh, K. Murata, K. Tokumura, K. Shudo, N. Miyata, and T. Okamoto, *Tetrahedron* **35**, 1059 (1979).

<sup>168</sup> B. L. Van Duuren, G. Witz, and S. C. Agarwal, *J. Org. Chem.* **39**, 1032 (1974).



(R = H) is singlet in character, the photochemistry of **64** was studied by Griffin *et al.*<sup>36</sup> Direct irradiation of **64** at 254 or 350 nm in benzene or acetone gave the phenanthrol **296** in essentially quantitative yield. Thermolysis of **64** at 200°C, however, yielded the isomeric phenanthrol **297**.

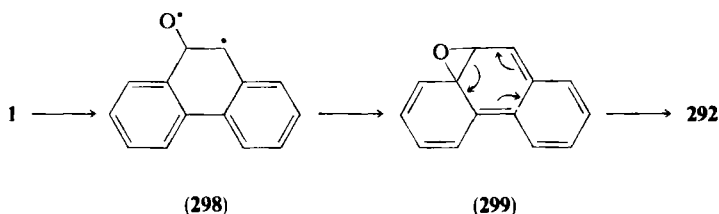


Wavelength-dependent photolysis<sup>169</sup> of **1** has been studied by Shudo and Okamoto. When **1** is irradiated at 300–350 nm in methylene chloride, a mixture containing 9-phenanthrol (50%), phenanthrene (11%), and the oxepin **292** (R = H, 0.5%) results. Irradiation of **1** at 207–235 nm, on the other hand, furnishes 56% of 9-phenanthrol, 0.2% of phenanthrene, 3% of **292** (R = H), and 0.2% of fluorene. Alternatively, irradiation at 250–290 nm with a low-pressure mercury lamp gives 8% of 9-phenanthrol, 20–30% **292** (R = H), 3% fluorene, and a dimer (~25%); no phenanthrene is observed under these conditions. Interestingly, two different excitations give 9-phenanthrol and the other excitation gives other products in a completely different way. Brightwell and Griffin suggested the mechanism in Scheme 4 for the conversion of **1** to **292** (R = H) photochemically.<sup>170</sup>

The formation of the oxepin is reasonably explained by an electrocyclic ring opening of rearranged epoxide **299** in a thermal reaction. As mentioned above, two routes to **299** are possible. If the rearrangement is concerted, a 1,5-sigmatropic reaction with inversion of the reaction center (oxygen) in **299** is photochemically allowed. It is possible to separate a nonconcerted process

<sup>169</sup> K. Shudo and T. Okamoto, *Chem. Pharm. Bull.* **21**, 2809 (1973).

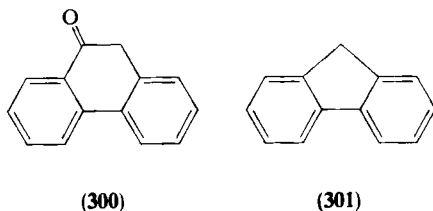
<sup>170</sup> N. E. Brightwell and G. W. Griffin, *J.C.S. Chem. Commun.*, 37 (1973).



SCHEME 4

involving a photochemical cleavage of the C—O bond to give diradical **298** or a dipole. This intermediate may attack the aromatic ring thermally to form epoxide **299** though such a process sacrifices aromaticity of two rings. Among the two mechanisms leading to **299**, the concerted mechanism looks more attractive because the overlap is favorable and the photochemical rearrangement to 9-phenanthrol seems to involve a cleavage of a C—O bond.

In the photochemical rearrangement of **1** at 77 K, Jerina *et al.* detected the keto tautomer **300** of 9-phenanthrol by IR.<sup>135</sup>



After a 3-hr exposure to light, the volatile components obtained by the oxidation of phenanthrene with singlet oxygen in a two-phase hexane–water system include fluorene (**301**), fluorenone, 9-phenanthrol, and 9,10-phenanthrenequinone. In certain runs an additional product, 2,2'-diformylbiphenyl, is detected. Under identical conditions, **1** undergoes interconversion to dibenzoxepin **292** (R = H, 9%) and 9-phenanthrol (~20%). Other products include fluorenone (3%), 2,2'-diformylbiphenyl (15%), 2-hydroxybiphenyl-2'-carboxylic acid lactone (16%), diphenic anhydride (4%), and 9,10-phenanthrenequinone (28%). Undoubtedly, hydration is a competing reaction as is photorearrangement to **292** (R = H) with both processes ultimately leading to reaction products.<sup>171</sup>

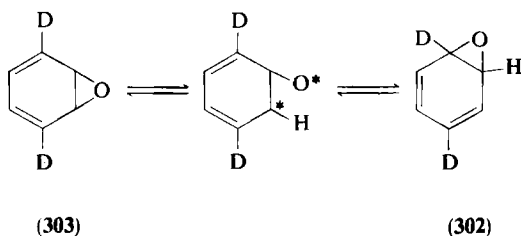
These results indicate that the sensitized photooxidation of phenanthrene in a two-phase hexane–water system involves the conversion of phenanthrene to **1**.

Phenanthrene, upon irradiation with a xenon lamp in the presence of nitrogen dioxide, produces 9,10-phenanthrenequinone and 9-hydroxy-10-

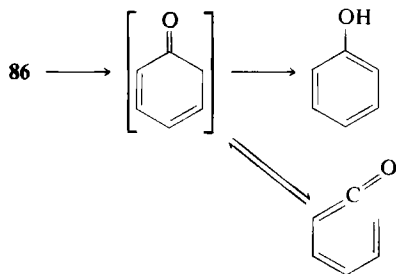
<sup>171</sup> B. J. Dowty, N. E. Brightwell, J. L. Laseter, and G. W. Griffin, *Biochem. Biophys. Res. Commun.* **57**, 452 (1974).

nitrophenanthrene. Alternatively, the same products are formed during photochemical and dark reactions of **1** with nitrogen dioxide in air. These results suggest that **1** could be an intermediate in the photochemical reactions of phenanthrene with nitrogen dioxide in air.<sup>172</sup>

The photochemical reaction of non-K-region oxides like dideuterated benzene oxide (**303**) and naphthalene 1,2-oxide has been studied at room temperature and at 77 K in acetone. When D-(**303**) is irradiated in acetone at room temperature, products corresponding to migration of the oxirane ring to the next position are obtained.



Ketenes have been detected as secondary photoproducts from the keto tautomers of **86** and **45**. Formation of the ketene, observed from **86**, implies that the keto tautomer of phenol is present, although below the limits of detection, during photolysis of **86** at 77 K.<sup>135</sup>

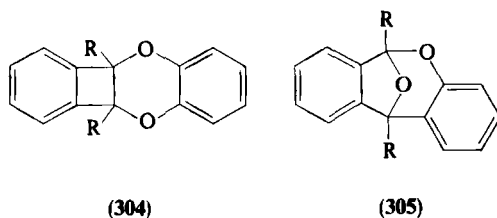


### 5. Reactions of Arene Oxides Derived from Acene Photooxides

The 9,10-diphenylanthracene photooxide **77**, on heating, releases oxygen almost quantitatively, whereas the unsubstituted or monoalkylated analogs (**75**) undergo essentially O—O bond cleavage, leading to degradation products or to rearranged isomers **304** and **305**.<sup>173</sup> Trapping experiments have shown that these isomers originate from the subsequent transformation of the

<sup>172</sup> K. Nojima, T. Ohya, S. Kanno, and M. Hirobe, *Chem. Pharm. Bull.* **30**, 4500 (1982).

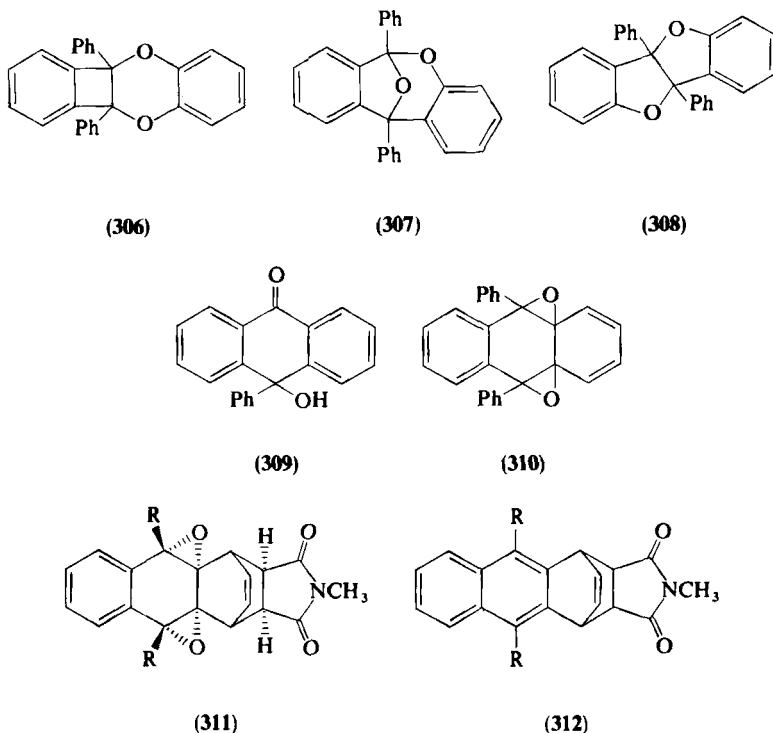
<sup>173</sup> J. Rigaudy, H. C. Parlat, D. Simon, and N. K. Cuong, *Bull. Soc. Chim. Fr.*, 493 (1976).



$R = H \text{ or } CH_3$

primary intermediates, namely, the *meso*-epoxides, which are unstable under these conditions.<sup>174</sup>

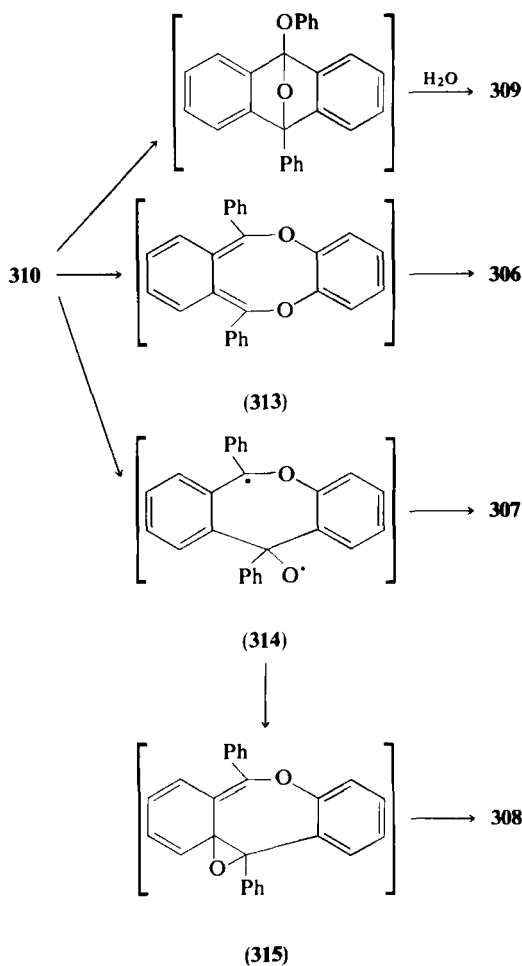
Endoperoxide **77** was subjected to UV irradiation under various conditions. Under these conditions five main products, **78**, **306**, **307**, **308**, and **309**, which are produced concurrently in variable proportions, were detected. Perhaps **306** is derived from the *meso*-diepoxide intermediate **310**. This diepoxide has been trapped by inclusion of a large excess of *N*-methylmaleimide (NMM) during irradiation of **77** in benzene at 20°C, using excitation of wavelengths



<sup>174</sup> J. Rigaudy, J. B.-Lafont, A. Dafoin, and N. K. Cuong, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **280**, 527 (1975).

greater than 400 nm. The structure for the 1:1 NMM adduct (**311**) has been described on the basis of its spectral data. On reduction with zinc and potassium iodide in aqueous acetic acid containing sodium acetate, **311** furnishes aromatized **312**.

When the same photolysis is carried out at  $-70^{\circ}\text{C}$  to get the *meso*-diepoxide **310**, warming to room temperature affords **306**. However, if a second irradiation at shorter wavelength is carried out during the warming period, a mixture containing only **307** and **308** is obtained. Based on these observations, Rigaudy *et al.*<sup>175</sup> have proposed the mechanism in Scheme 5, suggesting that

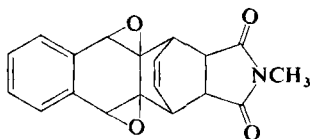


SCHEME 5

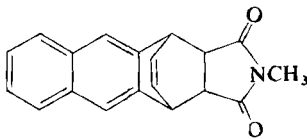
<sup>175</sup> J. Rigaudy, C. Breliere, and P. Scribe, *Tetrahedron Lett.*, 687 (1978).

**310**, which is formed first at longer wavelengths, rearranges thermally through the valence tautomer **313** to **306**. At shorter wavelengths, it undergoes photodimerization leading to **307** and **308**, possibly through intermediates **314** and **315**.

Unsubstituted anthracene photoxide **77**, unlike the diphenyl derivative **75**, is isomerized to the primary product **76** thermally. The *meso*-diepoxide **76** has been trapped by using NMM to furnish the 1:1 adduct **316**. As with **311**, **316** can also be reduced to *exo*-**317**.<sup>174</sup>

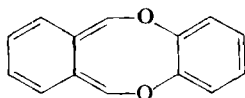


(316)

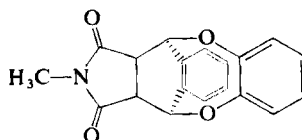


(317)

The *meso*-diepoxide **76** produces via valence tautomerism the unstable *o*-quinodimethane diether **318**, which also can be trapped by using NMM to give the 1:1 adduct **319**. Trapping of either **76** or **318** by dienophiles depends on the molar excess of the added dienophile. Depending on the dilution, the reaction



(318)



(319)

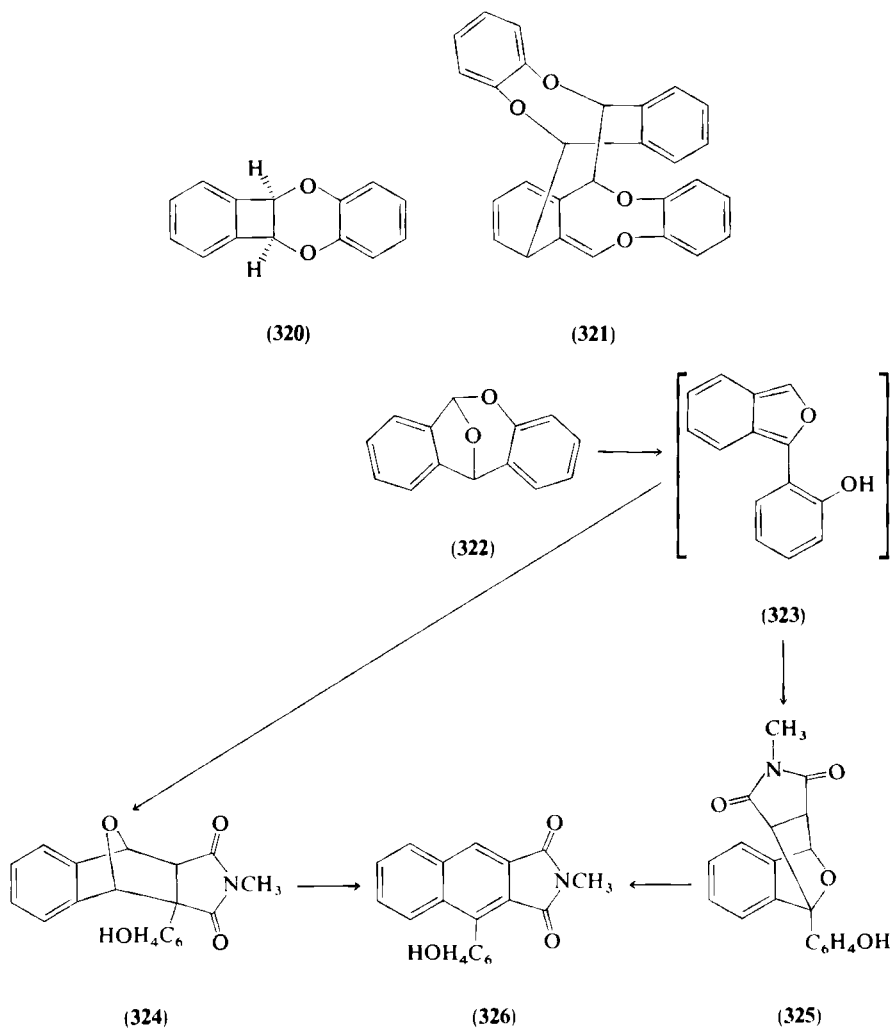
finally leads to the dimers of **318** or to its cyclized derivative **320**, besides anthraquinone in minor amounts.<sup>176</sup> The dimer **321** has been obtained in 70% yield by dropping a solution of **76** into boiling benzene.<sup>41</sup>

Addition of protic or Lewis acids to **76** leads to immediate isomerization. Thus **76** is transformed by picric acid or zinc chloride in dry benzene to the bicyclic acetal **322**. Stronger acids such as trifluoroacetic acid isomerize **322** further to the unstable isobenzofuran derivative **323**, which can be trapped with NMM in chloroform as a mixture of endo and exo adducts **324** and **325**, respectively, and the *in situ* dehydration product **326**.

Thermolysis of **75** in solution<sup>177</sup> can afford successively three dimers: **321**, **327**, and **328**. Their origin is the unstable diether **318**, which at 80°C dimerizes to **321** by an unusual ( $\pi 8_s + \pi 6_s$ ) concerted cycloaddition. Above 110°C, **321** isomerizes to **327** by a concerted 1,5-suprafacial sigmatropic migration.

<sup>176</sup> J. Rigaudy, J. B.-Lafont, A. Defoin, and N. K. Cuong, *Tetrahedron* **34**, 73 (1978).

<sup>177</sup> A. Defoin, J. B.-Lafont, J. Rigaudy, and J. Guilhem, *Tetrahedron* **34**, 83 (1978).



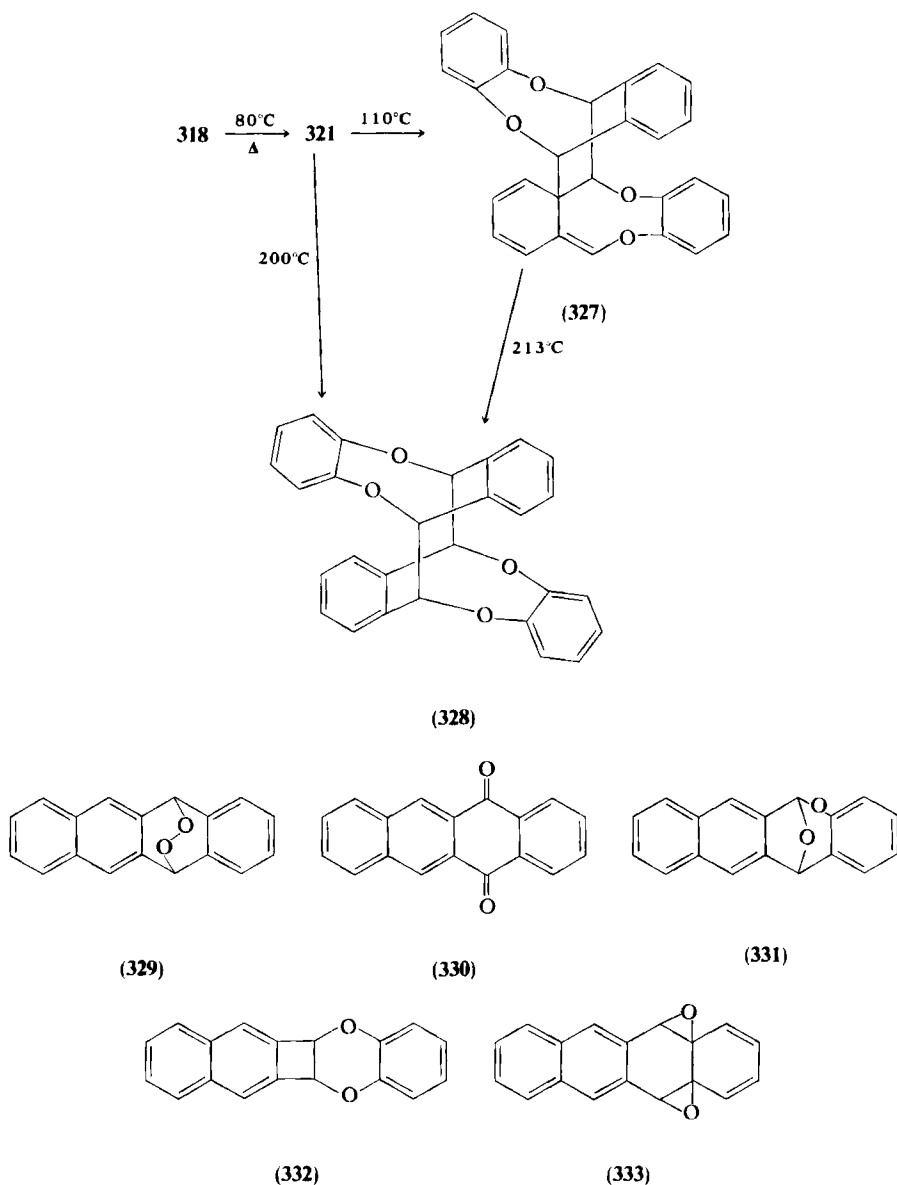
Finally, at higher temperatures ( $\sim 200^{\circ}\text{C}$ ) both dimers are partly converted to the symmetrical dimer **328**, probably by a radical pathway.

Similarly, thermolysis of naphthacene photooxide (**329**) leads to naphthacenequinone (**330**), the bicyclic acetal **331**, and the cyclobutene diether **332**.<sup>178</sup> These products are shown to have been formed by the involvement of the *meso*-diepoxide **333** by means of trapping experiments.

The influence of *meso*-phenyl substituents on the thermal behavior of naphthacenic endoperoxides is illustrated by a diversity of isomerization

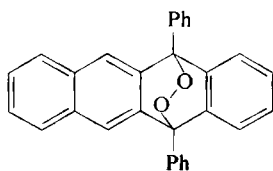
<sup>178</sup> J. Rigaudy and D. Sparfel, *Tetrahedron* **34**, 113 (1978).



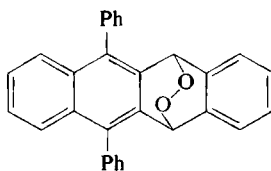


sequences that they undergo under thermolysis of the diphenyl derivatives 334 and 335.<sup>179</sup> Whereas 334 gives only the cyclobutenic diether 336, 335 leads to the bicyclic acetal 337 along with a dimer.

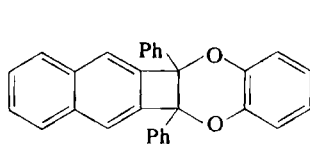
<sup>179</sup> J. Rigaudy and D. Sparfel, *Tetrahedron* **34**, 2263 (1978).



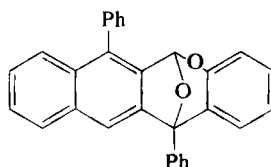
(334)



(335)



(336)



(337)

Thermolysis of variously substituted *meso*-pentacenic photooxides leads to various isomerizations that appear to be strongly affected by the phenyl substituents. These isomerizations also go through the intermediacy of *meso*-diepoxides.<sup>180</sup>

## VI. Arene Oxides as Intermediates in the Biosynthesis of Natural Products

Hydroxylation of aromatic rings is a very common and an important step in the biosynthesis of natural products.<sup>181,182</sup> Arene oxides were suggested as intermediates in the biosynthesis of natural products as early as in 1967.<sup>183</sup> However, not all hydroxylations proceed through arene oxides. A number of instances have been documented,<sup>184</sup> as in the case of cinnamic and benzoic acids, where ortho and para hydroxylations take place by the involvement of an NIH shift (arene oxides).

Involvement of arene oxides has been suggested in the biosynthesis of a number of natural products like **340** from **338** through intermediate **339**.<sup>185</sup> Formation of semiperivriol, totarol, ferruginol, and podocarpic acid from

<sup>180</sup> D. Sparfel, F. Gobert, and J. Rigaudy, *Tetrahedron* **36**, 2235 (1980).

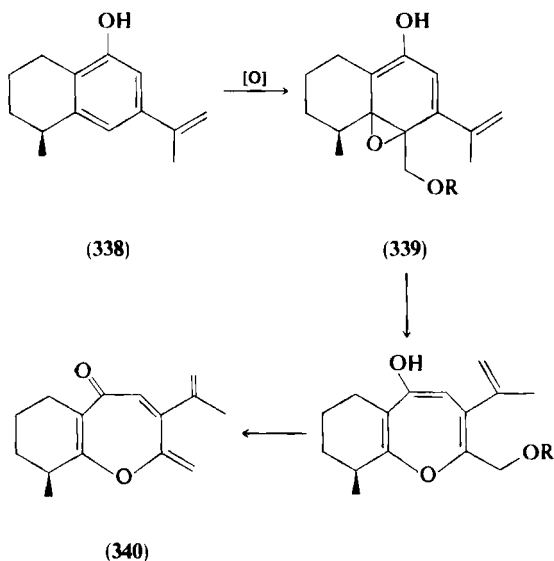
<sup>181</sup> A. R. Battersby, in "Oxidative Coupling of Phenols" (W. I. Taylor and A. R. Battersby, eds.), Chapter 3. Dekker, New York, 1978.

<sup>182</sup> T. Kametani and K. Fukumoto, *Synthesis*, 657 (1972).

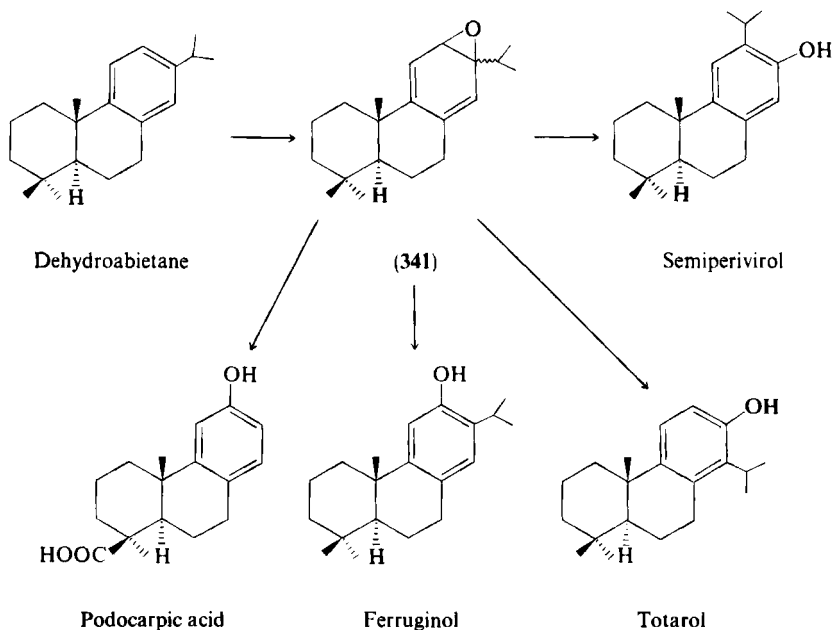
<sup>183</sup> D. H. R. Barton, *Chem. Br.* **3**, 330 (1967).

<sup>184</sup> A. Sutter and H. Grisebach, *Phytochemistry* **8**, 101 (1969).

<sup>185</sup> F. Bohlmann and W. R. Abraham, *Phytochemistry* **17**, 1629 (1978).

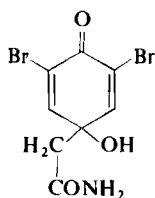


dehydroabietane proceeds through the involvement of arene oxide **341** or its oxygen position isomer.<sup>186</sup> Bromine-containing cyclohexadienol antibiotics

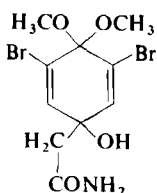


<sup>186</sup> E. Wenkert, J. de Pavia Campello, J. D. McChesney, and D. J. Watts, *Phytochemistry* **13**, 2545 (1974).

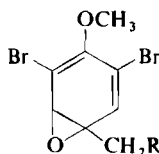
**342** and **343**, produced by certain marine sponges of the genera *Aplysina*, *Ianthella*, and *Verongia*, are believed to be biosynthesized by the intermediacy of arene oxides of type **344**.<sup>187</sup>



(342)

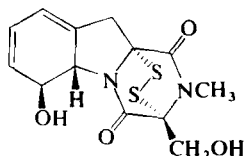


(343)

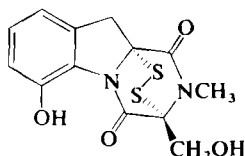


(344)

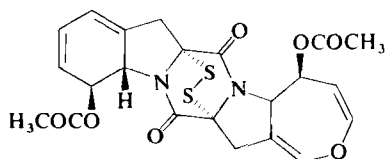
Arene oxides and their oxepin tautomers play a role in the biosynthesis of some microbial metabolites, e.g., the sulfur-containing antibiotics gliotoxin (**345**),<sup>188</sup> dehydrogliotoxin (**346**),<sup>189</sup> apoarontin (**347**),<sup>190</sup> aranotin (**348**),<sup>191</sup>



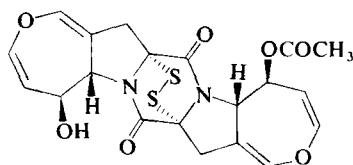
(345)



(346)



(347)



(348)

chaetocin (**349**),<sup>192</sup> and sporidesmin (**350**),<sup>193</sup> are biosynthesized through the involvement of epoxides or oxepins. These compounds are believed to originate from phenylalanine via arene oxides. The fungal metabolite LL-

<sup>187</sup> G. M. Sharma, B. Wig, and P. R. Burkholder, *J. Org. Chem.* **35**, 2823 (1972).

<sup>188</sup> M. R. Bell, J. R. Johnson, B. S. Wildi, and R. B. Woodward, *J. Am. Chem. Soc.* **80**, 1001 (1958).

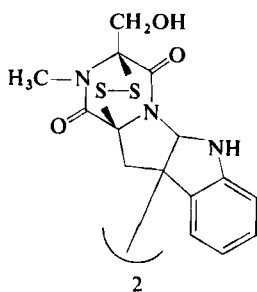
<sup>189</sup> G. Lowe, A. Taylor, and L. C. Vining, *J. Chem. Soc. C*, 1799 (1966).

<sup>190</sup> N. Neuss, R. Nagrajana, B. B. Molloy, and L. L. Huckstep, *Tetrahedron Lett.*, 4467 (1968).

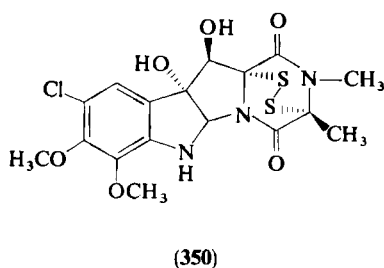
<sup>191</sup> R. Nagrajan, L. L. Huckstep, D. H. Lively, D. C. DeLong, M. M. Marsh, and N. Neuss, *J. Am. Chem. Soc.* **90**, 2980 (1968).

<sup>192</sup> D. Hauser, H. P. Weber, and H. P. Sigg, *Helv. Chim. Acta* **53**, 1061 (1970).

<sup>193</sup> R. Hodges, J. W. Ronaldson, A. Taylor, and E. P. White, *Chem. Ind. (London)*, 42 (1963).

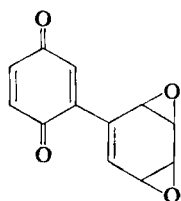


(349)

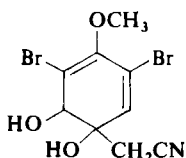


(350)

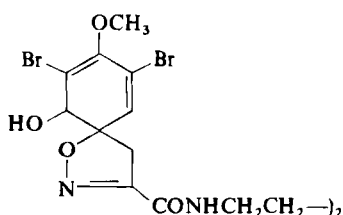
Z1220 (351) is shown to have a benzene dioxide structure.<sup>194</sup> Likewise, metabolites 352<sup>195</sup> and 353<sup>196</sup> from *Verongia* sponges were postulated to have been biosynthesized through arene oxides.



(351)



(352)



(353)

## VII. Arene Oxides and Cancer

One of the main points of interest in arene oxides arises from their biological reactions. At one time it was believed that arene oxides were the proximate intermediates responsible for carcinogenesis, mutagenesis, and necrosis. It will be useful to trace briefly the development of the current ideas of the involvement of arene oxides in carcinogenesis.

An early theory linking the structure of polycyclic aromatic hydrocarbons with carcinogenesis is the K-region theory of Pullman and Pullman,<sup>197,198</sup> according to which: (1) carcinogenic activity in aromatic hydrocarbons is determined by the existence of an active K-region, and (2) if the molecule

<sup>194</sup> D. B. Borders, P. Shu, and J. E. Lancaster, *J. Am. Chem. Soc.* **94**, 2540 (1972).

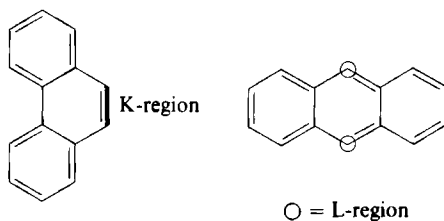
<sup>195</sup> E. Fattorusso and G. Sodano, *J.C.S. Perkin I*, 16 (1972).

<sup>196</sup> K. Moody, R. H. Thomson, E. Fattorusso, L. Minale, and G. Sodano, *J.C.S. Perkin I*, 18 (1972).

<sup>197</sup> A. Pullman and B. Pullman, *Adv. Cancer Res.* **3**, 117 (1955).

<sup>198</sup> W. C. Herndon, *Trans. N.Y. Acad. Sci.* [2] **36**, 200 (1974).

contains also an L-region, the supplementary condition requires that this region should be rather inactive. The K-region corresponds to a region of high  $\pi$ -bond order as the 9,10 bond in phenanthrene. An L-region corresponds to positions of very high reactivity as in the 9,10 positions of anthracene.



The K-region theory implies some form of an intermediate formed exclusively at the position representing the reactive metabolite in carcinogenesis. The importance of the L-region can be explained also on the basis of ready reactivity of those positions in competition with the K-region and the prior reactivity in the L-region, preventing further reaction at the K-region. All of these hypotheses have been well supported by experience derived from the chemical reactivities of K- and L-regions of polycyclic hydrocarbons. The K-regions react more readily than the other positions of the aromatic hydrocarbons. When an L-region is present, these sites are the most reactive and compete successfully with the K-region in the oxidative metabolism. When the L-regions undergo reactions to give quinones, they render the original K-region unreactive.

Reactions of K-region arene oxides derived from phenanthrene and 7,12-dimethylbenz[*a*]anthracene with nucleosides have been studied with a view to assessing the carcinogenicity of the products obtained.<sup>199</sup>

Conversion of arene oxides to dihydrodiols by mouse liver cytosol epoxide hydrolase and microsomal epoxide hydrolase has been compared, and it is found that the former is less active than the latter.<sup>200</sup>

10,11-Dibenz[*a,h*]anthracene epoxide has been made from the hydrocarbon chemically as well as by rat liver oxygenase. It failed to react chemically or enzymatically with glutathione.<sup>201</sup>

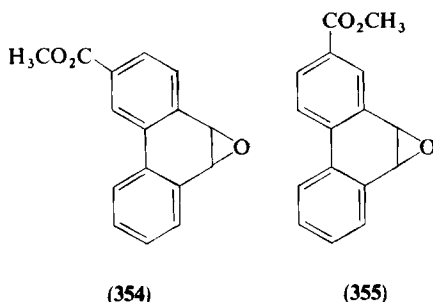
Miyata *et al.*<sup>202</sup> found that the order of mutagenicity of K-region arene oxides tested in *Salmonella typhimurium* strain TA 98 is **28** > **4** > **354**, **254** > **29** > **1**, **253**, **355**. Oxide **28** is most reactive, whereas **4** is also fairly active. In the nucleophilic reactions, **28** is more reactive in general. This fact might be linked to the strong mutagenicity of **28**. However, **29**, which is

<sup>199</sup> H. Friesel and E. Heeber, *Cancer Lett.* **3**, 169 (1977).

<sup>200</sup> F. Oesch and H. Golan, *Cancer Lett.* **9**, 169 (1980).

<sup>201</sup> P. Sims, *Biochem. J.* **130**, 27 (1972).

<sup>202</sup> N. Miyata, K. Shudo, Y. Kitahara, G. F. Haung, and T. Gramoto, *Mutat. Res.* **37**, 187 (1976) [*CA* **86**, 12529 (1977)].



as reactive as **28**, shows quite weak mutagenicity. The absence of a direct correlation between biological activity and acid-catalyzed reactivity ( $S_N1$  type) has been well established. The increasing order of the acid-catalyzed reactivity is shown together with the mutagenic activity (in parentheses) is **253** (–)  $\gg$  **29** ( $\pm$ )  $>$  **28** (+++)  $>$  **254** (+)  $>$  **1** (–)  $>$  **4** (++)  $\gg$  **355** (–)  $>$  **354** (+).

The least reactive (**354**) is mutagenic and the most reactive (**253**) is not mutagenic. This indicates that the chemical reactivity (both  $S_N1$  and  $S_N2$  reactions) forming a covalent carbon–nitrogen bond is not the only factor that determines the biological activity of arene oxides, though a certain minimum reactivity may be required.

All attempts to demonstrate that the K-region arene oxides are proximate or ultimate carcinogenic metabolites have been unsuccessful. The K-region arene oxides of benz[*a*]anthracene, 7-methylbenz[*a*]anthracene, 3-methylcholanthrene, and benzo[*a*]pyrene have much lower carcinogenic activity when compared to the parent hydrocarbons.<sup>203,204</sup> This fact argues against the K-region theory of Pullman and Pullman. Perhaps the strongest evidence against this theory comes from nucleic acid binding studies.<sup>205–207</sup> These results have established that the mechanism of binding of polycyclic aromatic hydrocarbons, like 7-methylbenz[*a*]anthracene to DNA in cells, do not involve K-region epoxides.

The K-region theory has been replaced by the theory of bay-region activation of polycyclic hydrocarbons to give mutagens and carcinogens.<sup>208</sup> A

<sup>203</sup> T. J. Slaga, A. Viaje, D. L. Berry, and W. Bracleen, *Cancer Lett.* **2**, 115 (1976).

<sup>204</sup> K. Burki, J. E. Wheeler, Y. Akamatsu, J. E. Scribner, G. Candelas, and E. Bresnick, *J. Natl. Cancer Inst. (U.S.)* **53**, 967 (1974).

<sup>205</sup> W. M. Baird, R. G. Harvey, and P. Brookes, *Cancer Res.* **35**, 54 (1975).

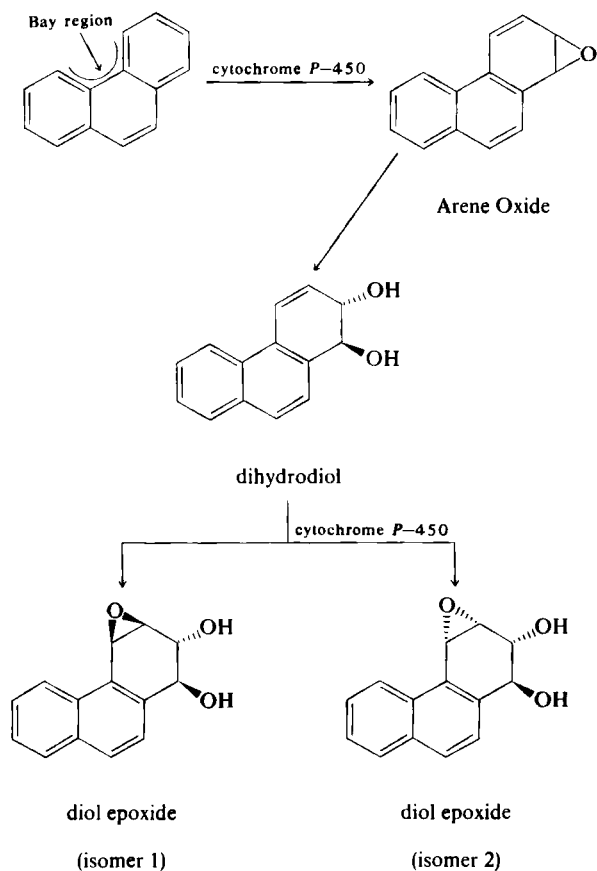
<sup>206</sup> W. M. Baird, A. Dipple, P. L. Grover, P. Sims, and P. Brookes, *Cancer Res.* **33**, 2386 (1973).

<sup>207</sup> S. H. Blabstein, I. B. Weinstein, D. Grunberger, J. Weisgras, and R. G. Harvey, *Biochemistry* **14**, 3451 (1975).

<sup>208</sup> D. M. Jerina, H. Yagi, D. R. Thakker, R. E. Lehr, A. W. Wood, W. Levin, and A. H. Conney, in "Microsomes, Drug Oxidations, and Chemical Carcinogenesis" (M. J. Coon, A. H. Conney, R. W. Estabrook, H. V. Gelboin, J. R. Gillette, and P. T. O'Brien, eds.), Vol. 2, p. 1041, and references cited therein. Academic Press, New York, 1980.

bay region is the "sterically hindered area which results when benzo ring is angularly fused to a polycyclic aromatic hydrocarbon."<sup>208</sup> According to this theory, the benzo ring diol epoxides in which the epoxide grouping forms part of the bay region of the hydrocarbon should be the most chemically reactive.

The diol epoxides are generally formed by epoxidation of the *trans*-diols formed by the opening of the arene oxide by epoxide hydrase. A mechanism for phenanthrene is illustrated in Scheme 6; absolute stereochemistry is not implied.<sup>208</sup>



SCHEME 6

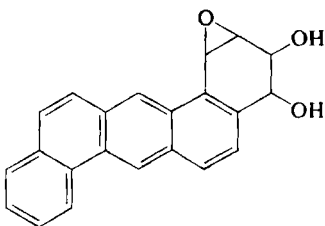
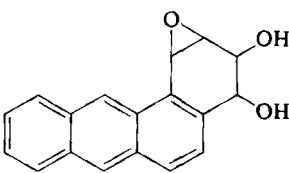
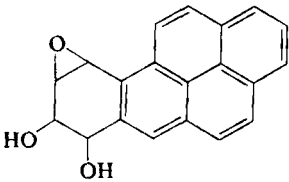
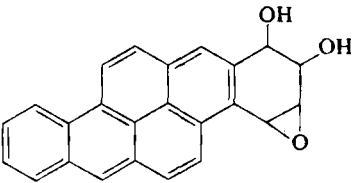
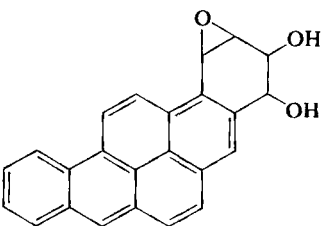
There is a correlation between the chemical reactivity of diol epoxides and relative carcinogenicity. The index of chemical reactivity has been taken as the ease of carbonium ion formation via spontaneous opening of the epoxide to the Zwitterion (Table XI).



TABLE XI  
COMPARISON OF PREDICTED CHEMICAL REACTIVITY OF BAY-REGION DIOL EPOXIDES  
WITH APPROXIMATE TUMORIGENICITY OF THE PARENT HYDROCARBON<sup>a</sup>

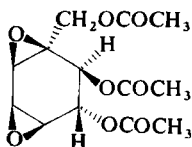
Diol epoxide	$E_{\text{deloc}}/\beta$	Approximate relative carcinogenicity
	0.600	+
	0.640	+
	0.658	-
	0.664	-
	0.714	-
	0.722	+

TABLE XI (cont.)  
COMPARISON OF PREDICTED CHEMICAL REACTIVITY OF BAY-REGION DIOL EPOXIDES  
WITH APPROXIMATE TUMORIGENICITY OF THE PARENT HYDROCARBON<sup>a</sup>

Diol epoxide	$E_{deloc}/\beta$	Approximate relative carcinogenicity
	0.738	+++
	0.766	±
	0.794	++++
	0.845	++++
	0.870	++++

<sup>a</sup> According to ref. 208.

Not all diol epoxides are necessarily carcinogenic in nature. Some of their derivatives are tumor inhibitors, e.g., the crotoepoxide **356** obtained from *Piper futokadzura*.<sup>209</sup>



(356)

### VIII. Arene Oxides in the Metabolism of Aromatic Compounds

A number of aromatic compounds are known to be metabolized by different tissues of the body, such as liver, lung, kidney, and bone marrow, where they are converted to arene oxides; e.g., bromobenzene<sup>210</sup> and benzene<sup>211,212</sup> are converted to the corresponding arene oxides during metabolism. Also, quinoline<sup>213</sup> is converted to the 5,6-dihydrodiol derived from the epoxide by cytochrome *P*-448-linked monooxygenases. On the other hand cytochrome *P*-450-linked mixed function oxygenases give quinoline 1-oxide. It has been shown that metabolism of naphthalene by rat liver involves formation of mono- and diepoxides.

Relatively stable arene oxides are the expected intermediates in the metabolism of halobenzenes to a variety of products.<sup>214</sup> Oxide **107** isomerizes exclusively to 2-chlorophenol, whereas **109** rearranges exclusively to 4-chlorophenol. Both **107** and **109** react with glutathione and are converted to *trans*-dihydrodiols.

The formation of 3-halophenols in the metabolism of chlorobenzene, bromobenzene, and fluorobenzene<sup>215</sup> cannot be explained on the basis of arene oxides as intermediates. These metabolites may represent examples of a direct hydroxylation of the ring. Besides, the magnitude of the isotopic effects observed during the metabolic formation of such meta-substituted phenols

<sup>209</sup> S. Takahashi, *Phytochemistry* **8**, 321 (1969).

<sup>210</sup> W. D. Reid and G. Krishna, *Exp. Mol. Pathol.* **18**, 80 (1973).

<sup>211</sup> R. Snyder and J. J. Kocsis, *CRC Crit. Rev. Biochem.* **3**, 265 (1975).

<sup>212</sup> L. S. Andrews, H. A. Sasame, and J. R. Gillette, *Life Sci.* **25**, 567 (1979).

<sup>213</sup> T. Tada, K. Takahashi, and Y. Kawazde, *Chem. Pharm. Bull.* **30**, 3884 (1982).

<sup>214</sup> J. R. L. Smith, B. A. J. Shaw, and D. M. Foulkes, *Xenobiotica* **2**, 215 (1972).

<sup>215</sup> J. Daly, D. Jerina, and B. Witkop, *Arch. Biochem. Biophys.* **128**, 517 (1968).

from deuterated nitrobenzene and phenyl methyl sulfone is also incompatible with the intermediacy of arene oxides. Such meta hydroxylations are not expected to be accompanied by the NIH shift.

In dilute solutions of purified microsomal epoxide hydrolase, the kinetics and thermodynamics of hydration of arene oxides<sup>216</sup> like **1** are similar. The epoxide hydrolase is sensitive to the stereochemistry of the substrate, as shown by the 40-fold differences in the rates of hydration of the (+) and (−) enantiomers of **28**.

Application of the exciton chirality rule has allowed the assignment of configuration (+)-*trans*-(4*R*,5*R*) to dihydroxy-4,5-dihydrobenzo[*a*]pyrene (**357**), a mammalian metabolite of benzo[*a*]pyrene.<sup>217</sup> Thus the prominent enantiomer of the 4,5-dihydrodiol formed from benzo[*a*]pyrene by rat-liver microsomes has the configuration (4*R*,5*R*) in contrast to the earlier report that the configuration was the opposite one.<sup>218</sup> Consequently, (+)-(**358**) has a (4*S*,5*R*) configuration. This epoxide is a better substrate for epoxide hydrolase than its enantiomer and has 1.5–5.5-fold less mutagenic activity as compared to the (−) enantiomer.

Phenanthrene is transformed to *trans*-9,10- (major), *trans*-1,2- (minor), and *trans*-3,4-dihydrodiol (minor) metabolites via monooxygenase-catalyzed formation of arene oxides, followed by epoxide hydrolase-catalyzed hydration in mammalian liver systems.<sup>219–221</sup> In bacterial cultures, phenanthrene is converted to *cis*-3,4- (major) and *cis*-1,2- dihydrodiols (minor) through the action of dioxygenase enzymes and molecular oxygen.<sup>221,222</sup> Recently, Boyd *et al.*<sup>70</sup> have prepared *trans*-3,4-dihydroxy-1,2,3,4-tetrahydrophenanthrene (**359**) and *cis*-3,4-dihydroxy-1,2,3,4-tetrahydrophenanthrene (**360**) in optically pure forms. These compounds have made possible the determination of the configurations of the *trans*- and *cis*-3,4-dihydrodiol metabolites of phenanthrene (**361** and **362**) as (−)-(3*R*,4*R*) and (+)-(3*S*,4*R*), respectively.

Epoxide hydrolase has been found to exhibit a marked enantiomeric selectivity toward the chiral K-region arene oxides **28**, **29**, and 3-bromophenanthrene 9,10-oxide (**363**) in detergent solutions. A 40-fold difference in the rate

<sup>216</sup> R. N. Armstrong, W. Levin, and D. M. Jerina, *Microsomes, Drug Oxid., Chem. Carcinog.* [Int. Symp. *Microsomes Drug Oxid.* 4th, 1979 Vol. 2, pp. 1117–1123 (1980).

<sup>217</sup> B. Kedzierski, D. R. Thakker, R. N. Armstrong, and D. M. Jerina, *Tetrahedron Lett.*, 405 (1981).

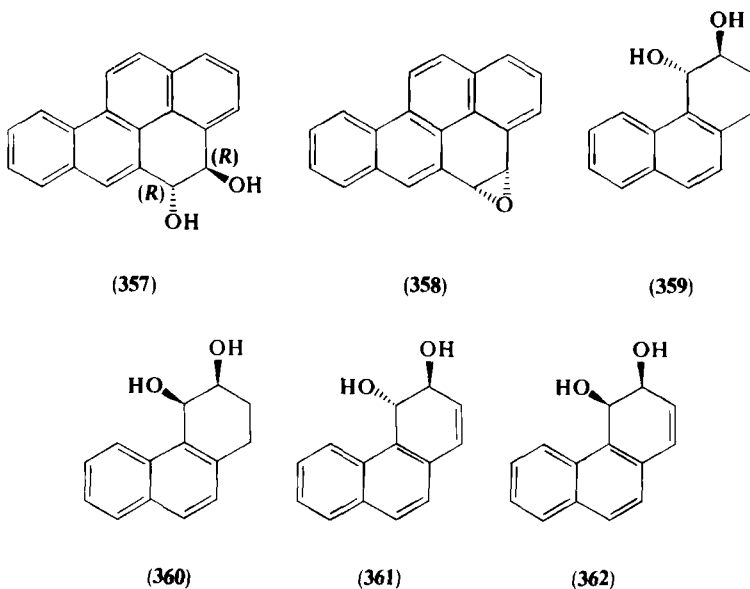
<sup>218</sup> S. K. Yang, P. P. Roller, and H. V. Gelboin, *Biochemistry* **16**, 3680 (1977).

<sup>219</sup> E. Boyland and G. Wolf, *Biochem. J.* **47**, 64 (1950).

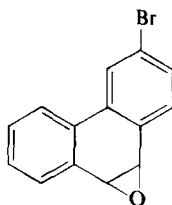
<sup>220</sup> E. Boyland and P. Sims, *Biochem. J.* **84**, 571 (1962).

<sup>221</sup> M. Koreeda, M. N. Akhtar, D. R. Boyd, J. D. Neill, D. T. Gibson, and D. M. Jerina, *J. Org. Chem.* **43**, 1023 (1978).

<sup>222</sup> D. M. Jerina, H. Selander, H. Yagi, M. C. Wells, J. F. Davey, V. Mahadevan, and D. T. Gibson, *J. Am. Chem. Soc.* **98**, 5988 (1976).



of hydration of (+)- and (–)-**28** is of particular significance, in view of the biological activity of this highly mutagenic K-region arene oxide.

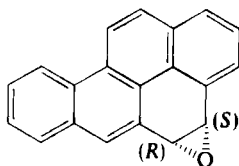


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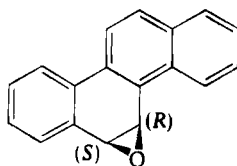
Armstrong *et al.*<sup>223</sup> have shown that nonenzymatic trans addition of glutathione to synthetic (+)-(4*S*,5*R*)- and (–)-(4*R*,5*S*)-benzo[*a*]pyrene 4,5-oxides (**364** and **365**) occurs at carbons 4 and 5 to give two diastereomeric pairs of positional isomers to almost equal extents. Correlations of the glutathione conjugates obtained from the 4,5-oxide derived from cytochrome *P*-450c-catalyzed oxidation of benzo[*a*]pyrene with those obtained from the syn-

<sup>223</sup> R. N. Armstrong, W. Levin, D. E. Ryan, P. E. Thomas, H. D. Mah, and D. M. Jerina, *Biochem. Biophys. Res. Commun.* **100**, 1077 (1981).

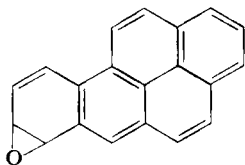
thetic enantiomers indicates that  $\geq 97\%$  of the enzymatically formed arene oxide is the (+)-(4*S*,5*R*) enantiomer (**364**).



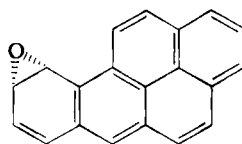
(364)



(365)



(366)



(367)

The stereospecific metabolism of racemic benzo[*a*]pyrene 4,5-, 7,8-, and 9,10-oxides (**28**, **366**, and **367**, respectively) by rat liver microsomes or highly purified epoxide hydrolase has been examined by Thakker *et al.*<sup>224</sup> The optical purity of the metabolically formed benzo[*a*]pyrene 7,8- and 9,10-dihydrodiols is relatively low (8 and 22%, respectively). The metabolically formed benzo[*a*]pyrene-4,5-dihydrodiol is highly enriched in the (–) enantiomer (78% optical purity). The low optical purity of benzo[*a*]pyrene-7,8-dihydrodiol is attributed to the ability of epoxide hydrolase to act upon position 8 of both optical isomers of **366** with almost equal ease.

A number of drugs having aromatic rings are metabolized by hydroxylation in the liver,<sup>225–227</sup> e.g., in the metabolism of mepivacaine (**368**), isomeric 3-hydroxy (**370**) and 4-hydroxy compounds have been isolated, out of which **370** has been shown to be formed through the involvement of arene oxide **369**.<sup>228</sup>

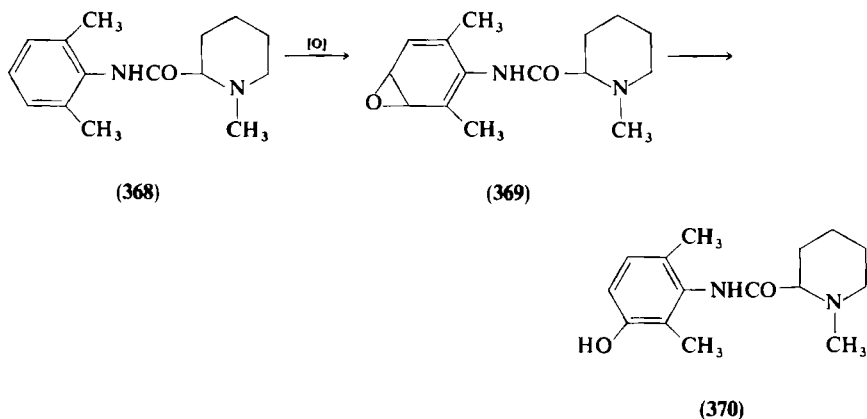
<sup>224</sup> D. R. Thakker, H. Yagi, W. Levin, A. Y. H. Lu, A. H. Conney, and D. M. Jerina, *J. Biol. Chem.* **252**, 6328 (1977).

<sup>225</sup> W. F. Trager, in "Concepts in Drug Metabolism" (P. Jenner and B. Testa, eds.), Part A, Chapter 3, p. 177. Dekker, New York, 1980.

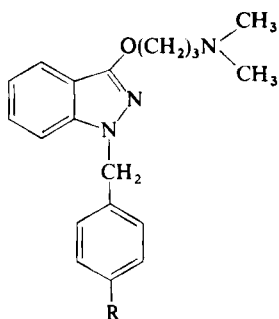
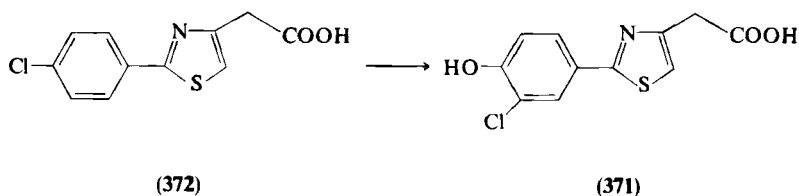
<sup>226</sup> B. Testa and P. Jenner, in "Concepts in Drug Metabolism" (P. Jenner and B. Testa, eds.), Part A, Chapter 2, p. 53. Dekker, New York, 1980.

<sup>227</sup> J. Edelson, D. P. Benziger, and J. F. Baker, *Annu. Rep. Med. Chem.* **17**, 333–342 (1982).

<sup>228</sup> P. J. Meffin and J. Thomas, *Xenobiotica* **3**, 625 (1973).



Also, formation of **371** as a metabolite from the antiinflammatory agent fencloic acid (**372**) involves an NIH shift (arene oxide).<sup>229</sup>



(373) R = H

(374) R = OH

Benzydamine (**373**), an analgesic and antiinflammatory drug, generates *p*-phenolic metabolite **374** despite several competing reactions.<sup>230</sup>

<sup>229</sup> D. M. Foulkes, *J. Pharmacol. Exp. Ther.* **172**, 115 (1970).

<sup>230</sup> N. S. Kataoka, K. Taira, T. Arira, T. Ariyoshi, and E. Takabatake, *Chem. Pharm. Bull.* **21**, 358 (1973).

Two important reactions of arene oxides in animal tissue are (1) detoxification and (2) formation of conjugates of arene oxides with purine pyrimidine bases of DNA. For both of these reactions to take place, the arene oxide should have a certain intrinsic stability to survive an aromatization reaction. Reaction with the thiolate bond of glutathione is responsible for detoxification, whereas the extent of involvement of arene oxides in the nucleophilic reactions with nonpolarized nitrogen bases of DNA is directly related to their carcinogenic activity.

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# Synthesis of Pyridines by Electrochemical Methods

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## I. Introduction

Whereas the first synthesis of chemicals by electrolysis dates back over 180 years, the equipment and techniques to understand the fundamentals of these reactions were not developed until recently. This review of electrochemical citations of pyridine compounds of industrial interest is keyed to the functionality of the starting pyridine; hence the electrochemistry of pyridines is indexed and not their preparation by electrolysis.

Because the electrochemistry of pyridines has not been reviewed before with regard to industrially significant processes, this review will therefore cover the period 1801–1983. Citations from 1801–1975 have been compiled in Swann's bibliography.<sup>1</sup> These citation listings were broken down into six indices: author, patent, product molecular formula, synonym, product name, and product type. A computer-aided search of *Chemical Abstracts* and the *World Patent Index* covered the period 1967–1983. Other sources such as the reviews on heterocyclic electrochemistry by Lund<sup>2</sup> and Nelson<sup>3</sup> contained useful citations. Nelson's review has a valuable table that summarizes the synthetic work by indexing the parent heterocycle.

Introductory treatments of electrochemistry have been published by both Weinberg<sup>4</sup> and Baizer.<sup>5</sup> A complementary book by Fry gives good insights into selected areas of electrochemistry, particularly with respect to voltammetry and electrode surface phenomena.<sup>6</sup> Lund has recently updated his earlier review of heterocyclic electrochemistry, and the literature is covered to 1982.<sup>2,7</sup>

## II. Cathodic Reactions

Over 90% of the reported studies on pyridine electrochemistry deal with cathodic transformations. One reason for this is that the experimental techniques for studying cathodic reactions are more numerous and tractable.

<sup>1</sup> S. Swann and R. Alkire, "Bibliography of Electro-organic Syntheses 1801–1975." Port City Press, Baltimore, Maryland, 1980.

<sup>2</sup> H. Lund, *Adv. Heterocycl. Chem.* **12**, 213–316 (1970); H. Lund, in "Organic Electrochemistry" (M. M. Baizer, ed.), Chapter 17. Dekker, New York, 1973.

<sup>3</sup> R. F. Nelson, *Tech. Chem. (N. Y.)* **5**, Part 2, 269 (1975).

<sup>4</sup> N. L. Weinberg, ed., "Techniques of Chemistry," Vol. 5, Part 1, Chapters 1–3. Wiley, New York, 1974; N. L. Weinberg and B. V. Tilak, eds., "Techniques of Chemistry," Vol. 5, Part 3, Chapters 1, 3–6, and 9–10. Wiley, New York, 1982.

<sup>5</sup> M. M. Baizer and H. Lund, eds., "Organic Electrochemistry." Dekker, New York, 1983.

<sup>6</sup> A. J. Fry, "Synthetic Organic Electrochemistry," Chapters 1–4 and 9. Harper & Row, New York, 1972.

<sup>7</sup> H. Lund and I. Tabaković, *Adv. Heterocycl. Chem.* **36**, 235–341, in press.

One-third of all pyridine electrochemical reports cite reduction of pyridinium quaternary salts. Such transformations have biochemical significance and the products are industrially important. Reductions of pyridine itself are next most frequent, although catalytic hydrogenation has largely replaced electrolytic reduction. Contrary to this trend, Robinson Brothers in England still claims to be reducing pyridine electrolytically on a large scale.<sup>8</sup> This process represents the largest scale commercial electrolysis of a pyridine compound reported to date. Reduction of other functionalities makes up the remaining citations; the least amount of work has been done on reduction of dihydropyridines, pyridones, hydroxyalkyl-, and aminoalkylpyridines. Only the reduction products of pyridones would seem to have any potential industrial significance. Unlike anodic reports, the research efforts in cathodic studies would appear to have been concentrated on those areas of industrial importance. Also in contrast to anodic citations, the mechanisms of reductive transformations have been studied in detail in many cases. Absorption and orientation effects at the electrode surface are well-known in selected cases.<sup>5,6</sup>

## A. PYRIDINE

There are other processes besides the production of piperidine that occur during cathodic transformations of pyridine. Depending on conditions, dimers, crossed hydrocoupling products, or polymers can be formed; these other products can also have a partially or fully reduced ring.

### 1. Piperidine

Voltammetry studies on pyridine and pyridine derivatives have delineated some of the initial mechanistic steps of reduction.<sup>9-11</sup> The half-wave potential was found to correlate with the  $n,\pi^*$  triplet energy.<sup>10</sup> The mechanism of pyridine reduction in liquid ammonia was studied by Talcott among others; this process was also studied on a synthetic scale.<sup>9,12</sup> Evidence for an ECE

<sup>8</sup> Robinson Brothers, British Patent 395,741 (1933); C. Jackson and A. T. Kuhn, in "Industrial Electrochemical Processes" (A. T. Kuhn, ed.), p. 512. Am. Elsevier, New York, 1971.

<sup>9</sup> C. L. Talcott, Ph.D. Thesis, University of California, Berkeley (1967); L. Yu-L. Teng, Ph.D. Thesis, University of Michigan, Ann Arbor (1976); K. Yasukouchi, J. Taniguchi, H. Yamaguchi, and M. Shiraishi, *J. Electroanal. Chem. Interfacial Electrochem.* **105**, 403 (1979).

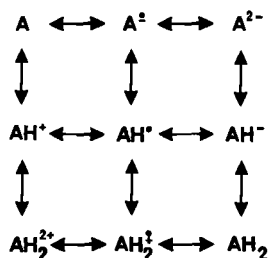
<sup>10</sup> R. O. Loutfy and R. O. Loutfy, *Can. J. Chem.* **51**, 1169 (1973).

<sup>11</sup> K. Zutshi and B. K. Bahl, *Proc. Semin. Electrochem.*, 14th, 1973, 254 (1974) [*CA* **82**, 161775 (1975)].

<sup>12</sup> O. R. Brown, R. J. Butterfield, and J. P. Millington, *Electrochim. Acta* **27**, 1665 (1982).

(Electron transfer, Chemical step, Electron transfer) mechanism in acetonitrile was proposed; the reduction products have been characterized.<sup>13</sup>

The possible mechanistic pathways can be shown using horizontal changes for electron transfer and vertical ones for proton transfer (Scheme 1). This scheme has been generalized and truncated to show only the reduction of A to  $AH_2$ . Pyridine reduction would be extended from this scheme to reflect the six electrons and six protons involved. Of course, protonated monocationic species would probably be important only in acidic electrolytes, whereas dianions would normally be formed only in aprotic electrolytes at high junction potentials. The dication,  $AH_2^{2+}$  is an unlikely species when A is pyridine.



SCHEME I

Reduction of pyridine by electrolytic methods is the oldest reported industrial process involving pyridine compounds. Merck patented this process in 1896; however, catalytic hydrogenation has supplanted this process for virtually every piperidine manufacturer.<sup>8,14,15</sup> The earliest report was by Ahrens, who described a process that others could not repeat.<sup>16</sup> Up to 1934 the technology was to use an aqueous sulfuric acid electrolyte and a lead cathode. Many of these reports are conflicting.<sup>17-19</sup> The interacting nature of electrochemical variables may be responsible in part for these discrepancies. Thus experimentation by an approach that attempts to hold all but one variable constant is bound to lead to different results depending on where the starting point was chosen or whether an important variable was, or was not,

<sup>13</sup> J. E. O'Reilly and P. J. Elving, *J. Am. Chem. Soc.* **94**, 7941 (1972); J. Nadra, H. Givadinovitch, and M. Devand, *J. Chem. Res., Synop.*, 192 (1983).

<sup>14</sup> E. Merck & Co., German Patents 90, 308 (1896) and 104,644 (1898).

<sup>15</sup> M. Windholz, ed., "The Merck Index," 9th ed., p. 7261. Merck & Co., Rahway, New Jersey, 1976.

<sup>16</sup> F. B. Ahrens, *Z. Elektrochem.* **2**, 577 (1896); L. Pincussohn, *Z. Anorg. Allg. Chem.* **14**, 379 (1897); F. P. Doane, B. S. Thesis, Massachusetts Institute of Technology, Cambridge (1920).

<sup>17</sup> C. Marie and G. Lejeune, *J. Chim. Phys. Phys.-Chim. Biol.* **22**, 59 (1925).

<sup>18</sup> N. S. Drozdov, *J. Gen. Chem. USSR (Engl. Transl.)* **3**, 351 (1933).

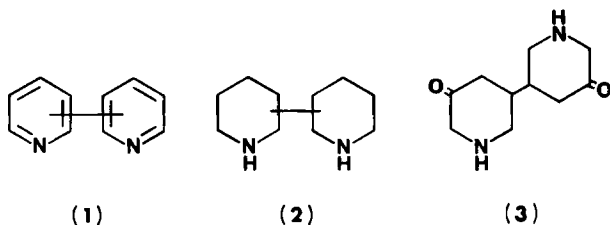
<sup>19</sup> D. W. Parkes, U.S. Patent 1,947,732 [*CA* **28**, 2628 (1934)].

controlled. Electroorganic process citations can be hard to repeat, sometimes because of the large number of important variables that are involved and occasionally because some of these important variables are unrecognized. For these reasons, confirmation of previous studies can be tenuous.

A study of different cathode materials appeared that showed that a high hydrogen overpotential was needed and that also presaged work using a catalytic electrode surface.<sup>20</sup> Later work by Swann and co-workers indicated that the type of carbon cathode was important, coke and lampblack giving almost no high-boiling products.<sup>21</sup> Reduction of pyridine under many conditions leads to dimeric reduced products (see below); however, reduction at a Raney nickel cathode was reported to give piperidine in excellent yield. Even when the reduction was stopped at intermediate stages, no partially reduced or dimeric products were found.<sup>22</sup> Previously reported work on an ordinary nickel cathode indicated that the surface was easily poisoned and would not maintain high current efficiencies.<sup>23-25</sup>

## 2. Dimeric Products

The production of bipyridyls (1) and bipiperidyls (2) was observed on reduction of pyridine. Schering AG has a patent on a process for producing 4,4'-dipyridyls at the cathode of a divided or undivided cell using liquid ammonia as the solvent.<sup>26</sup> The same bipyridyl was also formed during electrolysis of bromobenzene in pyridine solvent, using Mg electrodes.<sup>27</sup> Bipiperidyls (2) were observed as products of pyridine reduction as early as



<sup>20</sup> S. Szmaragd and E. Briner, *Helv. Chim. Acta* **32**, 553 (1949).

<sup>21</sup> S. Swann, C. Y. Chen, and H. D. Kerfman, *J. Electrochem. Soc.* **99**, 460 (1952).

<sup>22</sup> I. V. Kirilyus, G. K. Murzatova, and D. V. Sokol'skii, *Elektrokhimiya* **15**, 1543 (1979) [*CA* **92**, 58570 (1980)]; Russian Patent 657,026 (1979).

<sup>23</sup> Z. Alaune and A. Lazauskiene, *Liet. TSR Mokslu Akad. Darb., Ser. B* (1), 59 (1970) [*CA* **73**, 83066 (1970)].

<sup>24</sup> Z. Alaune and A. Lazauskiene, *Liet. TSR Mokslu Akad. Darb., Ser. B* (3), 105 (1969) [*CA* **72**, 38222 (1970)].

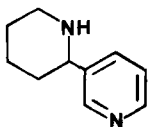
<sup>25</sup> N. I. Kobozev and V. V. Monblanova, *J. Phys. Chem. Moscow* **7**, 645 (1936).

<sup>26</sup> K. Junghans, U.S. Patent 4,194,046 (1980) [*CA* **92**, 6421 (1980)].

<sup>27</sup> T. T. Tsai, W. E. McEwen, and J. Kleinberg, *J. Org. Chem.* **26**, 318 (1961).

1913.<sup>28</sup> Only the 2,2'- and 4,4'-bipiperidyl (2) were reported at that time; however, later studies report the 2,4'-isomer as one of the products.<sup>29</sup> Recent work suggests that acidic reduction of pyridine gives not only 4,4'-bipyridine (1) as well as 2,2'-(1) and bipiperidyl (2), but also the diketone (3).<sup>30</sup> The structure of this product is apparently in error because the authors report a carbonyl stretching frequency ( $1400\text{--}1590\text{ cm}^{-1}$ ) that is inconsistent with a cyclic ketone. The calculated  $m/e$  peaks are incorrect, and the reported fragmentation pattern is unexpected. A better formulation of this material would perhaps be an open-chain structure.

Mechanistic studies on the reduction of the isomeric bipyridines (1) have been done.<sup>31,32</sup> The generation of radical anions and dianions in liquid ammonia was studied and a mechanism was proposed for the electrolysis of 2,2'-bipyridine (1) in basic solution. In addition, the macroscale reduction of the symmetrical isomers of 1 was studied, and the ease of reduction followed the order  $2,2' = 4,4' > 3,3'$ -(1).<sup>33</sup> Various electrode materials were examined. The reduction products of 2,2'- and 3,3'-bipyridine (1) at various cathodes were found to consist of roughly equal amounts of both the threo and erythro stereoisomers. Reduction of anabasine (4) gave the unsymmetrical 2,3'-bipiperidyl (2).<sup>34</sup>



(4)

<sup>28</sup> B. Emmert, *Ber. Dtsch. Chem. Ges.*, **46**, 1716 (1913).

<sup>29</sup> E. P. Hart, *J. Chem. Soc.*, 3872 (1953).

<sup>30</sup> G. A. Tolkacheva, A. A. Ziyaev, and E. Abibova, *Sb. Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* (**595**), 87 (1979) [*CA* **95**, 14934 (1981)].

<sup>31</sup> O. R. Brown and R. J. Butterfield, *Electrochim. Acta* **27**, 321 (1982); A. M. Shaldybaeva, E. A. Mambetkaziev, and S. I. Zhandov, *Prikl. Teor. Khim.* (**4**), 356 (1973) [*CA* **83**, 67932 (1975)]; L. Roullier and E. Laviron, *Electrochim. Acta* **22**, 669 (1977); E. A. Mambetkaziev, S. I. Zhdanov, B. B. Damaskin, V. N. Statsyuk, A. Shaldybaeva, and B. Tuleutaev, *Nov. Polyarogr. Tezisy Dokl. Vses. Soveshch. Polyarogr.*, **6th**, 1975, 117 (1975) [*CA* **86**, 23503 (1977)].

<sup>31a</sup> N. K. Kiva, V. M. Artemova, L. V. Dulenko, and F. I. Kogan, *Tezisy Dokl. Vses. Soveshch. Polyarogr.*, **7th**, 1978, 66 (1978) [*CA* **92**, 205998 (1980)]. [*CA* **86**, 23503 (1977)].

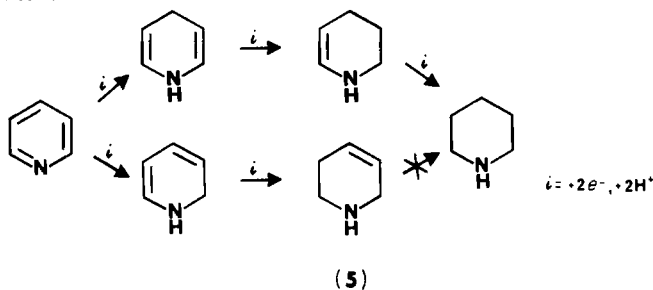
<sup>32</sup> H. Erhard and W. Jaenicke, *J. Electroanal. Chem.* **65**, 675 (1975); **81**, 89 (1977).

<sup>33</sup> Yu. N. Forostyan, A. P. Oleinik, and V. M. Artemova, *Elektrokhimiya* **7**, 715 (1971); V. M. Artemova, Yu. N. Forostyan, V. G. Govorukha, and E. I. Forostyan, *ibid.* **12**, 1816 (1976); Yu. N. Forostyan, E. I. Lyushina, V. M. Artemova, and V. G. Govorukha, *ibid.*, **73**; N. K. Akhmetov, R. I. Kaganovitch, B. B. Damaskin, and E. A. Mambetkaziev, *ibid.* **14**, 1761 (1978).

<sup>34</sup> Yu. N. Forostyan and G. V. Lazur'evskii, *Tr. Khim. Prir. Soedin.* (**2**), 53 (1959) [*CA* **55**, 27307 (1961)].

### 3. Partial Reduction Products

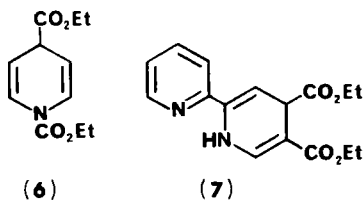
Few reports on the electrolytic reduction of pyridine mention the isolation of partially reduced products. The only one observed to date has been the 3-piperideine (**5**). Ferles attributed the presence of **5** to concurrent reduction mechanisms, one which led to this product and the other to piperidine (Scheme 2).<sup>35</sup> Thus, if the first-formed intermediate was a 1,4-dihydro product, then full reduction to piperidine occurred, but if the intermediate was a 1,2-dihydro product, then the olefin was formed. The 3-piperideine (**5**) would not be further reduced under the conditions. The concept of competing pathways at an initial step in the reduction mechanism is probably sound, but the proposal of 1,2- versus 1,4-dihydro intermediates has not been fully substantiated.



SCHEME 2

### 4. Condensation Products

Two different types of coupling processes have been cited for pyridine. The first involves the carboxylation and subsequent alkylation of the carboxylate salt to form the 1,4-dihydro-1,4-dicarboxyalkyl product (**6**). Reductive carboxylation of 2,2'-bipyridyl (**1**) followed a slightly different pathway, giving the 1,4-dihydro-4,5-dicarboxyethyl product (**7**).<sup>36</sup> Apparently, steric factors favor electrophilic attack on the  $\beta$  carbon.

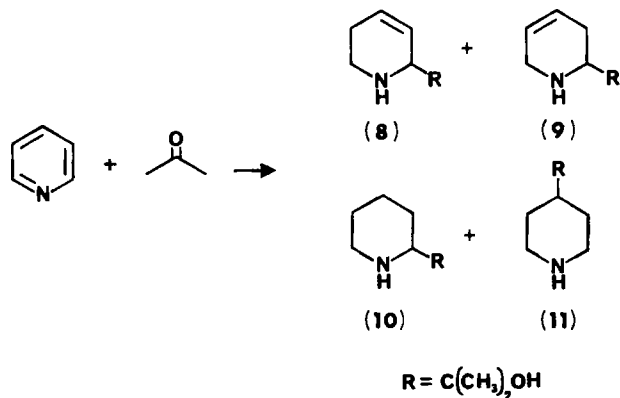


<sup>35</sup> M. Ferles, *Collect. Czech. Chem. Commun.* **24**, 1029 (1959).

<sup>36</sup> D. Michelet, French Patent 2,444,030 [CA **94**, 164821 (1981)].

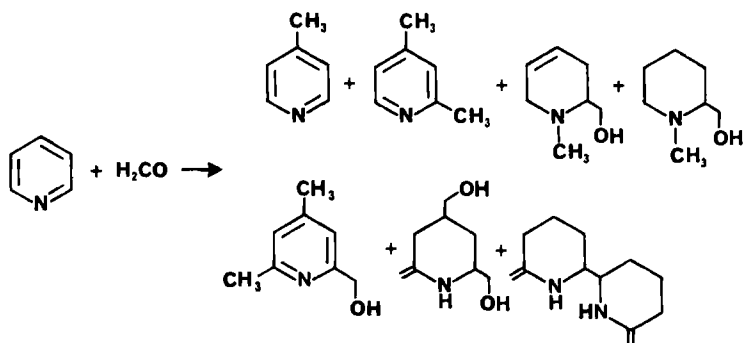


Hydrocoupling of aldehydes and ketones with pyridine during reduction is a facile process. The products are piperidyl carbinols substituted in the 2- or 4-position of the ring. They can also have a double bond at the 3-position (Scheme 3). Different workers reported varying amounts of the possible



SCHEME 3

isomers. For instance, Ferles and co-workers indicated that the reaction in Scheme 3 gave rise to **8** and **11**, whereas Nonaka and Sugino reported identifying isomers **8–10**.<sup>37–39a</sup> The product ratios and distributions are sensitive to the type of cathode, solvent, and other parameters.<sup>39,39a</sup> The products from hydrocoupling of aldehydes with pyridine were more varied and some of them resulted from multiple reactions (Scheme 4).<sup>39a,40</sup>



SCHEME 4

<sup>37</sup> M. Ferles, M. Vanka, and A. Silhankova, *Collect. Czech. Chem. Commun.* **33**, 2108 (1969).

<sup>38</sup> T. Nonaka and K. Sugino, *J. Electrochem. Soc.* **116**, 615 (1969).

<sup>39</sup> T. Nonaka, T. Sekine, K. Odo, and K. Sugino *Electrochim. Acta* **22**, 271 (1977).

<sup>39a</sup> T. Nonaka and K. Sugino, *Denki Kagaku* **38**, 105 (1970) [*CA* **75**, 44223 (1971)].

<sup>40</sup> T. Nonaka, S. Miyajima and K. Odo, *Denki Kagaku* **41**, 142 (1973) [*CA* **79**, 4677 (1973)].

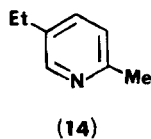
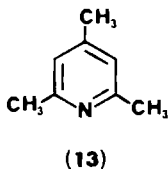
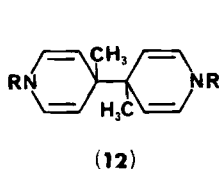
Hydrocoupling of acetaldehyde and pyridine gave rise to no less than 16 identified products. Some of the reported products are commercially interesting; therefore, techniques for controlling selectivity would be valuable.

### 5. Polymeric Products

The preparation of polyamines directly from a "monomer" like pyridine has commercial interest because the resulting polymer would be a base resin with a potentially high capacity. Universal Oil has patented the process by which a polypyridine was made.<sup>41</sup> Possible structures for pyridine polymers were proposed.<sup>42</sup> The influence of  $\text{Be}^{2+}$  and  $\text{Mg}^{2+}$  was also studied.<sup>43</sup>

### B. ALKYL PYRIDINES

The reduction of alkylpyridines follows a course similar to the reduction of pyridine itself.<sup>11</sup> However, the stereochemistry is important when disubstituted piperidines are made. All the same types of products were seen as with reduction of pyridine, and the technology was largely the same. Fundamental studies show that the  $E_{1/2}$  was still correlated with the  $n, \pi^*$  triplet energies.<sup>10</sup> The radical anions of alkylpyridines formed in liquid ammonia behaved similarly to those derived from pyridine except that increased alkyl substitution made the radical anion more stable.<sup>9</sup> The synthetic work on pyridine dimers in liquid ammonia also included work on 4-picoline, which gave the tetrahydrobipyridine and which, after N-alkylation, yielded **12**.<sup>12</sup> An approximate lifetime of the 4-picoline radical anion was given. Voltammetry of the symmetrical collidine (**13**) was studied at impregnated graphite electrodes, with hydrophobic impregnating agents giving the most reproducible results.<sup>31a</sup> Studies on the orientation of a pyridine at the electrode surface were done on a system for electrocatalytic production of hydrogen.<sup>44</sup> Reorienta-



<sup>41</sup> J. J. Louvar, U.S. Patent 3,574,072 [CA 75, 21481 (1971)].

<sup>42</sup> A. Cisak and P. J. Elving, *Electrochim. Acta* 10, 935 (1965).

<sup>43</sup> Ya. S. Vasina, G. F. Astakhova, R. F. Karysheva, and A. I. Fedorova, *Elektrokhimiya* 4, 468 (1968).

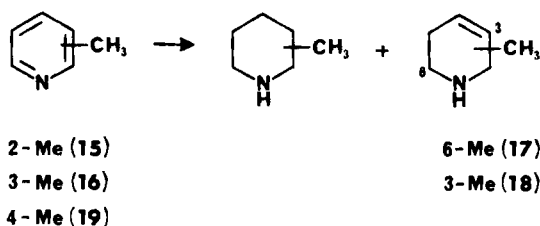
<sup>44</sup> S. G. Mairanovskii and A. P. Churilina, *Elektrokhimiya* 12, 728 (1976).

tion of 2-methyl-5-ethylpyridine (14) from normal to the electrode surface to flat was noted.

The polymers of alkylpyridines were covered in the previously cited patent on pyridine polymers.<sup>41</sup> Formation of alkylbipyridyls was likewise covered in previous papers.<sup>26</sup>

### 1. Alkylpiperidines and Alkylpiperidineines

Ferles *et al.* have studied the reduction of alkylpyridines and reported the yields of piperidines and 3-piperidineines. For instance, reduction of either 2-picoline (15) or 3-picoline (16) gave predominantly the respective piperidines; it also gave significant amounts of the piperidineines 17 and 18, respectively (Scheme 5) (Table I).<sup>35</sup> Other isomeric piperidineines were not formed, and the



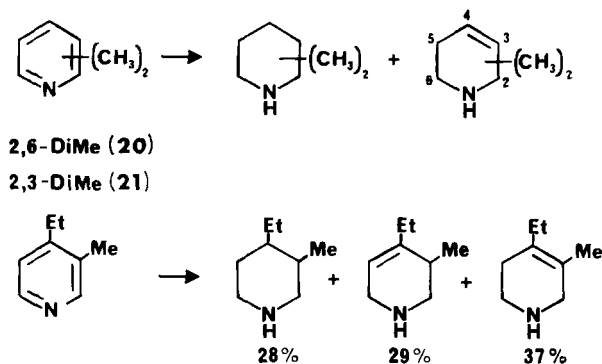
SCHEME 5

selectivity was explained on the basis of forming either the 1,2-dihydro or 1,4-dihydro products initially (see Scheme 2). Reduction of 4-picoline (19) gave more olefin than either 15 or 16, which was to be expected (Table I). A later report showed that 3-ethylpyridine gave both isomeric olefins in roughly the same ratio, which is in direct contrast to the results from reduction of 16.<sup>45</sup>

TABLE I  
THE PRODUCT DISTRIBUTION FROM ELECTROCHEMICAL  
REDUCTION OF THE ISOMERIC PICOLINES

Picoline	Yield (%)	
	Methylpiperidine	Methylpiperidineine
2-Methyl (15)	66	24 [6-Methyl (17)]
3-Methyl (16)	67	22 [3-Methyl (18)]
4-Methyl (19)	58	39

<sup>45</sup> M. Ferles, H. Havel, and A. Tesarova, *Collect. Czech. Chem. Commun.* **31**, 4121 (1966).



SCHEME 6

Reduction of the isomeric lutidines was also studied (Scheme 6).<sup>34,46,47</sup> In some cases the products were only *cis* as in reduction of 2,6-lutidine (20), and in other cases the products were mixtures of stereoisomers, as in 2,3-lutidine (21). When alkyl substituents were in the 3,4- or 3,5-positions, piperidine products were predominant (Table II). Reduction of the symmetrical collidine (13) gave various piperidine isomers of which the all-*cis* (22) was predominant.<sup>48</sup> However, the 3-olefin 23 was the major product. The thermodynamically less stable piperidines 24 and 25 were found in significant yield.

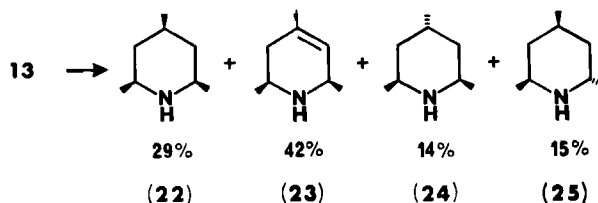
TABLE II  
THE PRODUCT DISTRIBUTION FROM ELECTROCHEMICAL  
REDUCTION OF THE ISOMERIC LUTIDINES

Lutidine	Yield (%)	
	Piperidine	3-Piperidine
2,6-Dimethyl (20)	77 ( <i>cis</i> )	21 ( <i>cis</i> )
2,3-Dimethyl (21)	64 ( <i>cis</i> and <i>trans</i> )	29 ( <i>cis</i> - and <i>trans</i> -5,6-Dimethyl)
2,5-Dimethyl	55	45 (3,6-Dimethyl)
3,4-Dimethyl	34	28 (4,5-Dimethyl)
		30 (3,4-Dimethyl)
3,5-Dimethyl	58	42 (3,5-Dimethyl)

<sup>46</sup> M. Ferles and A. Silhankova, *Z. Chem.* **8**, 175 (1968).

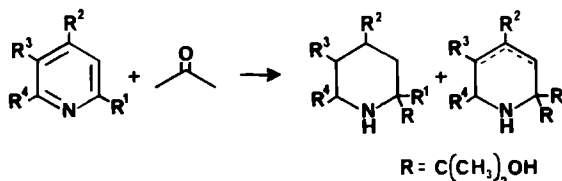
<sup>47</sup> A. Silhankova, D. Doskocilova, and M. Ferles, *Collect. Czech. Chem. Commun.* **34**, 1976 (1969).

<sup>48</sup> A. Silhankova, D. Doskocilova, and M. Ferles, *Collect. Czech. Chem. Commun.* **34**, 1895 (1969).



## 2. Hydrocoupling Products

The products of coupling of alkylpyridines with ketones follows the same course as for pyridine itself except that the relative position of substitution is now of interest.<sup>37,39,39a</sup> Coupling seemed to take place preferentially in the 2- or 6-position but would also occur in the 4-position, especially when both the 2- and 6-positions were blocked with alkyl groups (Scheme 7) (Table III). Hydrocoupling with aldehydes was also studied.<sup>39,39a</sup>



SCHEME 7

TABLE III  
HYDROCOUPLING OF ALKYLPIRIDINES WITH ACETONE

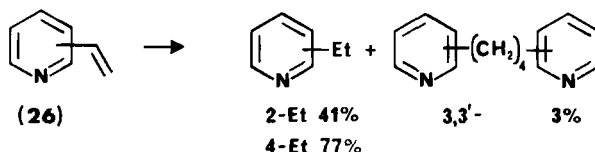
Substituent on pyridine of Scheme 7				Current efficiency (%)	
R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Piperidine	3- and 4-Piperideine
H	H	H	Me	4	41
H	H	Me	H	7	51
H	Me	H	H	1	68
H	Et	H	H	1	67
H	<i>i</i> -Pr	H	H	1	64
H	Me	H	Me	2	38
Me	H	H	Me	3	22
Me	Me	H	Me	—	14

## C. VINYL PYRIDINES

The olefinic group of vinylpyridines undergoes a variety of reactions, which include reduction to the ethane, addition reactions, dimerizations, and polymerizations. There are few voltammetry studies on the isomeric vinylpyridines (26). The reduction of the bisquaternary salt of 1,2-di(2-pyridyl)-ethylene has been studied, and the role of adsorption and autoinhibition during reduction of 1,2-di(4-pyridyl)ethylene was also determined.<sup>49,50</sup>

1. *Pyridylethanes*

Both 2- and 4-(26) were reduced at a mercury cathode in aqueous sulfuric acid to give the saturated ethane (Scheme 8).<sup>51</sup> A small amount of dimer was reported for reduction of 3-(26). Volke and Holubek report both synthetic and



SCHEME 8

mechanistic work on the reduction of various 1,2-dipyridylethylenes where the position of ring attachment had an influence on the product distribution.<sup>52</sup> The relative ease of reduction followed the pattern expected from the study of 26 itself where the order was found to be 4- > 2- > 3-substitution. Thus in this study the order was 4,4'- > 2,4'- > 2,2'- > 3,4'- > 2,3'-substitution. Synthetic yields of the ethane were generally high.

2. *Addition Reactions*

Only one report concerning addition reactions was found, but it exemplifies the potential synthetic utility of such a strategy; more work should be done using these methods.<sup>53</sup> 2-Styrylpyridine (27) can be acylated in fair yield (or carboxylated, depending on the electrophile used) (Scheme 9). Some saturated

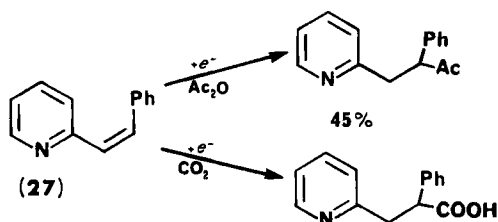
<sup>49</sup> S. Hünig and H.-C. Steinmetzer, *Tetrahedron Lett.* (47), 4835 (1972).

<sup>50</sup> E. Laviron and B. Riollot, *Bull. Soc. Chim. Fr.* (12), 5077 (1968).

<sup>51</sup> T. Nonaka, T. Kato, T. Fuchigani, and T. Sekine, *Electrochim. Acta* 26, 887 (1981).

<sup>52</sup> J. Volke and J. Holubek, *Collect. Czech. Chem. Commun.* 27, 1777 (1962).

<sup>53</sup> H. Lund and C. Degrand, *Acta Chem. Scand., Ser. B* B33, 57 (1979).

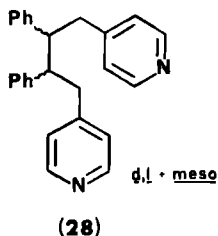


SCHEME 9

ethane product was formed as well as hydrodimers. 4-Styrylpyridine was also studied, and the product distribution was more complex, bisacylated and enol acetate products being formed.

### 3. Hydrodimers

Both 2- and 4-(26) yielded the saturated hydrodimers using Baizer's procedure.<sup>54</sup> Utley and Caddy confirmed the macroscale synthesis of the hydrodimer of 4-(26).<sup>55</sup> 4-Styrylpyridine gave the isomeric *meso* and *dl* hydrodimers (28) as did the *p*-tolyl and *p*-anisyl analogs of styrylpyridine.<sup>56</sup>



### 4. Polymers

The only isomer that has been studied is 4-(26). The polymerization was effected in either ammonia solvent or in a solvent-free system.<sup>57</sup> An anionic mechanism was proposed, and molecular weights were in the range of 10,000 to 260,000. As expected, higher current densities led to lower average molecular weights.

<sup>54</sup> J. D. Anderson, M. M. Baizer, and E. J. Prill, *J. Org. Chem.* **30**, 1645 (1965).

<sup>55</sup> D. E. Caddy and J. H. P. Utley, *Tetrahedron* **34**, 331 (1978).

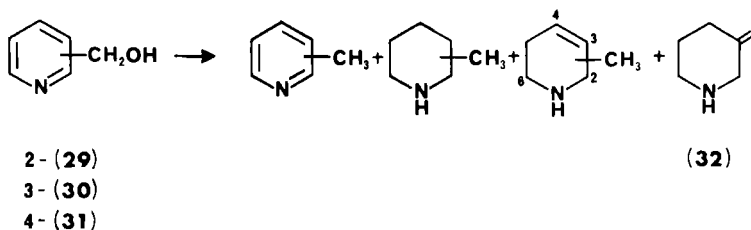
<sup>56</sup> K. Alwair, J. F. Archer, and J. Grimshaw, *J.C.S. Perkin II*, (11), 1663 (1972).

<sup>57</sup> D. Laurin and G. Parravano, *J. Polym. Sci., Part B* **4**, 797 (1966); D. Laurin, Ph.D. Thesis, University of Michigan, Ann Arbor (1967); D. Laurin and G. Parravano, *J. Polym. Sci., Part C* (22), 103 (1968).

## D. HYDROXYALKYLPYRIDINES

Very little work has been done on reduction of hydroxyalkylpyridines, although the approach can be an excellent way to make alkylpyridines from the carbinols. Work done points up once again how variable the products of a given transformation can be with seemingly small changes in experimental conditions.

Reduction of the three isomeric pyridylcarbinols (**29–31**) (Scheme 10) leads to products similar to reduction of the hydrocarbon parents **15**, **16**, and **19** (Scheme 5).<sup>58</sup> One should note, however, that the product ratios are different (Table IV). In the case of the 3-isomer (**30**), the unsaturated product (**32**) is exocyclic in this report, whereas it is endocyclic (**18**) in a previous report of the reduction of  $\beta$ -picoline (**16**). Ferles and Tesarova give IR evidence for **32** here and identify **18** by derivatization.<sup>35</sup> The IR evidence would seem to be more valid. In contrast to **30**, the 3-pyridylmethylcarbinol (**33**) gave endocyclic piperideines **34** and **35** (Scheme 11). For the pyridylmethylcarbinols **36** and **37**, the product ratios were different and the 3-isomer (**36**) gave a mixture of exocyclic and endocyclic piperideines, but mostly exo-(**38**) (Scheme 12).



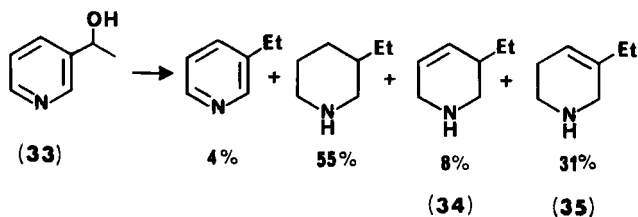
SCHEME 10

TABLE IV  
 THE PRODUCT DISTRIBUTION FROM ELECTROCHEMICAL REDUCTION OF THE  
 ISOMERIC HYDROXYMETHYLPYRIDINES

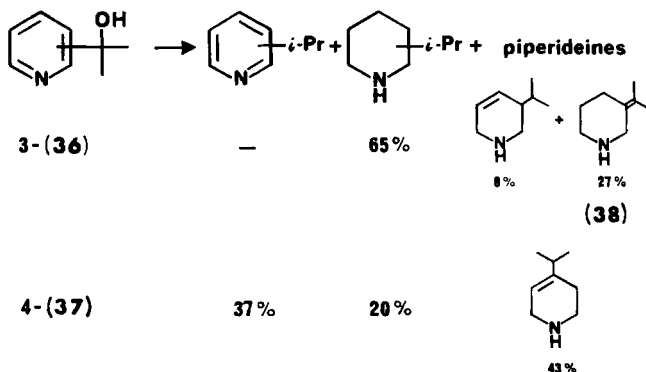
Hydroxymethylpyridine	Yield (%)		
	Picoline	Methyl-3-piperideine	Methylpiperidine
2-Carbinol ( <b>29</b> )	25	16 (6-Methyl)	37
3-Carbinol ( <b>30</b> )	2	26 [( <b>32</b> ) in Scheme 10]	34
4-Carbinol ( <b>31</b> )	7	63	20

<sup>58</sup> M. Ferles and A. Tesarova, *Collect. Czech. Chem. Commun.* **32**, 1631 (1967).





SCHEME 11



SCHEME 12

Reduction of optically active pyridylcarbinols showed interesting behavior. The 2-isomer (**39**) retained chirality in the product alkylpyridine, whereas the 4-isomer (**40**) did not (Table V) (Scheme 13).<sup>59</sup> A mechanism was proposed previous to this work to account for the retention of chirality in **39**.<sup>60</sup>

Acylated pyridylcarbinols having a vicinal nitro group can undergo reductive elimination to the olefin.<sup>61</sup> In most cases the yields were good as long as the hydroxy group was protected.

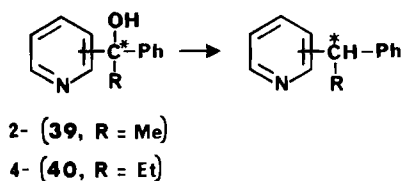
TABLE V  
HYDROGENOLYSIS OF CHIRAL HYDROXYALKYLPYRIDINES

Hydroxyalkylpyridine (Scheme 13)	Alkylpyridine (yield, %)	$[\alpha]_D^{20}$ (MeOH)
2-( <b>39</b> , R = Me)	62	$-0.1^\circ \pm 0.1^\circ$
4-( <b>40</b> , R = Et)	94	$-5.0^\circ \pm 0.2^\circ$

<sup>59</sup> T. Nonaka, T. Ota, and T. Fuchigami, *Bull. Chem. Soc. Jpn.* **50**, 2965 (1977).

<sup>60</sup> T. Nonaka, T. Amakawa, and K. Odo, *Denki Kagaku* **40**, 100 (1972) [*CA* **77**, 55614 (1972)].

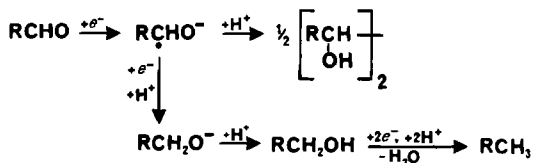
<sup>61</sup> A. Petsom and H. Lund, *Acta Chem. Scand., Ser. B* **B34**, 614 (1980).



SCHEME 13

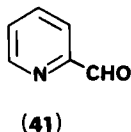
## E. ALDEHYDES

Aldehydes can be reduced in a one-electron step to give a dimeric product, or pinacol (Scheme 14). The radical anion monomer yields the carbinol, which can be further reduced to the hydrocarbon (see Section II,D). Control of the experimental conditions allows one to achieve selectivity, and the major product can be any one of these three possibilities.



SCHEME 14

Pyridyl aldehydes are reduced by a mechanism involving a preequilibrium in aqueous electrolytes.<sup>62,63</sup> The rate-determining step for reduction was found to be the ionization of the *gem*-diol, or hydrated aldehyde. As a consequence, buffers were found to have an effect on the reduction of the 2-aldehyde (**41**).<sup>64</sup>



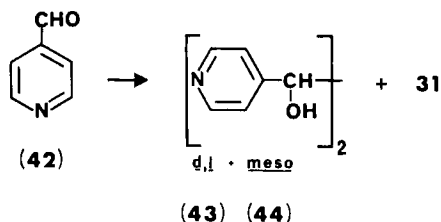
The 4-aldehyde (**42**) was reduced to a mixture of the 4-carbinol (**31**), and both the *dl*- and *meso*-pinacols (**43** and **44**, respectively) (Scheme 15).<sup>65</sup> The

<sup>62</sup> J. F. Rusling, Ph.D. Thesis, Clarkson College of Technology, Potsdam, New York (1980); J. Segretario, J. F. Rusling, and P. Zuman, *J. Electroanal. Chem. Interfacial Electrochem.* **117**, 341 (1981).

<sup>63</sup> J. F. Rusling and P. Zuman, *J. Electroanal. Chem. Interfacial Electrochem.* **143**, 289 (1983).

<sup>64</sup> J. F. Rusling and P. Zuman, *Anal. Chem.* **52**, 2209 (1980).

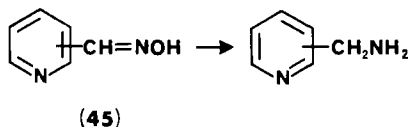
<sup>65</sup> J. F. Rusling and P. Zuman, *J. Org. Chem.* **46**, 1906 (1981).



SCHEME 15

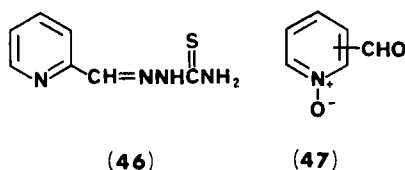
yield of carbinol **31** was dependent on the junction potential and the pH of the electrolyte, best conditions being acidic pH and relatively high potential. The ratio of **44** to **43** increased with increasing pH and increasing potential.

Mechanistic work has been done on reduction of all three aldehyde oximes **45**; the products of macroscale reduction are the picolylamines (Scheme 16).<sup>66</sup> These amines are more conveniently made from the nitrile at present because the aldehyde precursor is difficult to make.



SCHEME 16

The thiosemicarbazone of the 2-aldehyde (**46**) was studied by voltammetry, and the imine bond was found to be electroactive.<sup>67</sup> Neither the 2- nor the 4-aldehyde *N*-oxide [2-(**47**) and 4-(**47**)] was reduced as expected, rather the aldehyde and the *N*-oxide were reduced together.<sup>68</sup> The 3-aldehyde *N*-oxide [3-(**47**)] was reduced normally, giving the carbinol *N*-oxide.



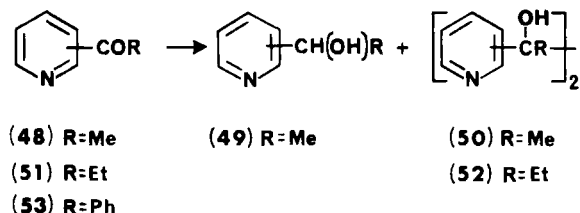
<sup>66</sup> S. F. Baron, Ph.D. Thesis, Rutgers University, New Brunswick, New Jersey (1969); J. Volke, R. Kubiček, and F. Šantavý, *Collect. Czech. Chem. Commun.* **25**, 871 (1960).

<sup>67</sup> J. F. Arenas, M. Cortijo, and E. Garcia, *An. Quim., Ser. A* **77**, 219 (1981) [*CA* **97**, 30206 (1982)]; J. C. Vire, R. L. De Jager, D. G. Dupont, G. J. Patriarche, and G. D. Christian, *Fresenius' Z. Anal. Chem.* **307**, 277 (1981) [*CA* **95**, 88186 (1981)].

<sup>68</sup> E. Laviron and R. Gavasso, *Talanta* **16**, 293 (1969).

## F. KETONES

The larger part of the work on ketones concerns the reduction of the isomeric acetylpyridines (**48**). The products were the carbinols (**49**) and pinacols (**50**) (Scheme 17); there are no reports of alkylpyridine products, as were seen in carbinol reductions (see Section II,D). In acidic media, reduction of 2-(**48**) gave almost exclusively 2-(**49**) and little dimer.<sup>69</sup> What dimer was formed was mostly meso and the proportion of it increased as pH increased.



SCHEME 17

Increasing junction potential also increased carbinol yield as was seen with aldehyde reductions. In basic electrolytes or in nonaqueous media, the dimer **50** was the major product.

Asymmetric induction during the reduction of 4-(**48**) was observed when a surface-modified carbon cathode was used.<sup>70</sup> Optical yields were low but the effect of the chiral amino acid bound to the carbon surface was proved to be a true surface phenomenon. Induction of chirality by homogeneous rather than surface-bound agents has also been studied.<sup>71</sup> All the isomeric acetylpyridines (**48**) were reduced in the presence of three different chiral alkaloids. Both carbinol products 2- and 4-(**49**) were shown to possess induced chirality, but the 3-carbinol (**49**) had none under any of the conditions tried. More rapid protonation of the intermediate was proposed to account for the lack of induced chirality. Optimization of optical yields was done.<sup>72</sup> The pinacols (**50**) formed along with **49** were found to have no induced chirality. Optical yields have been as high as 50%.<sup>73</sup> The role of electroabsorption was found to be important in the reduction of 2-(**48**).<sup>74</sup> Product distributions were noted as a function of surfactant present in the electrolyte, carbinol **49** being favored

<sup>69</sup> R. M. Jenevein, Ph.D. Thesis, Louisiana State University, Baton Range (1969); J. H. Stocker and R. M. Jenevein, *J. Org. Chem.* **34**, 2807 (1969).

<sup>70</sup> B. F. Watkins, J. R. Behling, E. Kariv, and L. L. Miller, *J. Am. Chem. Soc.* **97**, 3549 (1969).

<sup>71</sup> J. Kopilov, S. Shatzmiller, and E. Kariv, *Electrochim. Acta* **21**, 535 (1976).

<sup>72</sup> J. Kopilov, E. Kariv, and L. L. Miller, *J. Am. Chem. Soc.* **99**, 3450 (1977).

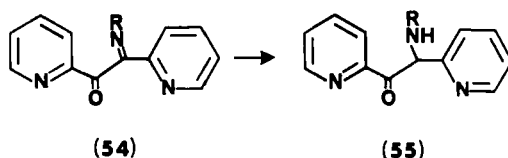
<sup>73</sup> J. Hermolin, J. Kopilov, and E. Gileadi, *J. Electroanal. Chem. Interfacial Electrochem.* **71**, 245 (1976).

<sup>74</sup> K. Koester, P. Riemenschneider, and H. Wendt, *Isr. J. Chem.* **18**, 141 (1979).

when surfactant was present.<sup>75</sup> The effect of electrode materials has also been reported.<sup>76</sup> The optical yield was best on Hg or Pb and poor on Cd, C, Zn, or Sb.

Production of pinacols (**50**) in preference to carbinols (**49**) has also received interest. All three isomers of **48** were studied by Allen and Cohen and found to give the respective dimer **50** in good yield.<sup>77</sup> Reduction of 3-(**48**) to give 3,3'-(**50**) was examined further and the rearrangement to the pinacolone analog was done.<sup>78</sup>

Reduction of ketones other than **48** to dimers has been examined. Ethyl pyridyl ketone (**51**) gave a poor yield of the corresponding pinacol (**52**).<sup>79</sup> Pinacols can also be made from crossed coupling of ketones with 3-(**48**).<sup>80</sup> Finally, a study of the radical anions formed from the isomeric benzoylpyridines (**53**) was done, and the rates of rotation of the pyridyl ring were determined.<sup>81</sup> The mechanism of reduction of the oxime and thiosemicarbazone derivatives of **53** was determined by voltammetry techniques.<sup>82</sup> The monoimine derivative of the pyridil **54** was reduced to the  $\alpha$ -amino ketone **55** (Scheme 18).<sup>83</sup> Unsaturated pyridyl ketones and heteroaryl pyridyl ketones have also been studied by voltammetry.<sup>84,85</sup>



SCHEME 18

## G. CARBOXYLIC ACIDS, ESTERS, AMIDES, AND NITRILES

Not a great deal of work has been done on the acid or ester reduction mechanisms. There is no fundamental reason why a carboxylic acid should not be reduced electrolytically just as easily as the ester or amide. However, one

<sup>75</sup> K. Koester and H. Wendt, *J. Electroanal. Chem. Interfacial Electrochem.* **138**, 209 (1982).

<sup>76</sup> H. Wendt, *Angew. Chem., Int. Ed. Engl.* **21**, 256 (1982).

<sup>77</sup> M. J. Allen and H. Cohen, *J. Electrochem. Soc.* **106**, 451 (1959).

<sup>78</sup> R. G. Vdovina, I. V. Alekseev, Zh. P. Trifonova, and A. V. Karpova, *Zh. Prikl. Khim.* **38**, 2607 (1965); M. J. Allen, *J. Org. Chem.* **15**, 435 (1959).

<sup>79</sup> M. J. Allen, H. Cohen, W. G. Pierson, and J. A. Siragusa, *J. Chem. Soc.*, 757 (1961).

<sup>80</sup> M. J. Allen, W. G. Pierson, and J. A. Siragusa, *J. Chem. Soc.*, 2081 (1961); T. Shono, H. Ohmizu, and S. Kawakami, *Tetrahedron Lett.* (**42**), 4091 (1979).

<sup>81</sup> A. J. L. Sevenster and B. J. Tabner, *J.C.S. Perkin II*, 1148 (1981).

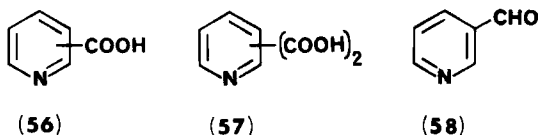
<sup>82</sup> M. A. Gomez-Nieto, M. C. Luque de Castro, and M. Valcárcel, *Electrochim. Acta* **28**, 325, 435 (1982).

<sup>83</sup> J. Holubek and J. Volke, *Collect. Czech. Chem. Commun.* **25**, 3292 (1960).

<sup>84</sup> C. Degrand, P. L. Compagnon, and M. Lacour, *Electrochim. Acta* **23**, 705 (1978).

<sup>85</sup> R. Naef, *Helv. Chim. Acta* **65**, 1734 (1982).

study of all three isomeric monoacids (**56**) indicated only hydrogen evolution catalyzed by the carboxylic acid.<sup>86</sup> Another report indicated that a ring reduction process is involved that is dependent on the solution pH.<sup>87</sup> Neither case showed the results of a macroscale reduction, so that the claim of the product distribution would seem to be premature. Acidity constants on the six possible isomeric dicarboxylic acids were determined by polarography.<sup>88</sup> The diacids (**57**) were claimed to undergo more normal reductive processes than the monoacids (**56**).<sup>89</sup> Esters of nicotinic acid [3-(**56**)] were reduced in 50% aqueous ethanol; again, the products were not analyzed.<sup>89</sup> Lund described methods for translating polarographic results into macroscale predictions, at least for derivatives of isonicotinic acid [4-(**56**)].<sup>90</sup>



Macroscale reduction of the monoacids **56** could lead to a variety of products, depending on the extent of electrolysis. For instance, reduction to the carbinols (**29–31**) would seem likely; further reduction might also give the picolines **15**, **16**, and **19**. Reduction of the picolines could also give the piperidines or piperdeines (see Schemes 5 and 10). Experimentally, all of these processes have been observed at one time or another in addition to formation of the isomeric aldehydes **41**, **42**, and **58**.

The earliest citations contain the reports of the most extensive electrolysis. Thus reduction of the 4-acid **56** gave aliphatic aldehydes and ammonia due to ring cleavage.<sup>91</sup> The survival of the aldehyde functionality during a reductive pyridine ring cleavage is surprising. A study of the three isomeric acids **56** by Sorm did not indicate ring-opened products but rather the picolines and their reduced products (Scheme 5).<sup>92</sup> The 2- and 4-(**56**) isomers gave, in addition, the unsaturated pipecolic acids **59** and **60**, respectively. The isomer 3-**56** gave the fully saturated material (**61**). Ferles and Prystas essentially confirmed these results but also reported the fully saturated pipecolic acid from the reduction of 2-(**56**) as well as the 4-olefin (**62**).<sup>93</sup> Also, the reduction of the 3-ester **63**

<sup>86</sup> L. Campanella and G. De Angelis, *Rev. Roum. Chim.* **16**, 545 (1971).

<sup>87</sup> A. G. Pozdeeva and E. G. Novikov, *Zh. Prikl. Khim.* **40**, 213 (1967); J. Volke and V. Volkova, *Collect. Czech. Chem. Commun.* **20**, 1332 (1955).

<sup>88</sup> C. Tissier and M. Agoutin, *J. Electroanal. Chem. Interfacial Electrochem.* **47**, 499 (1973).

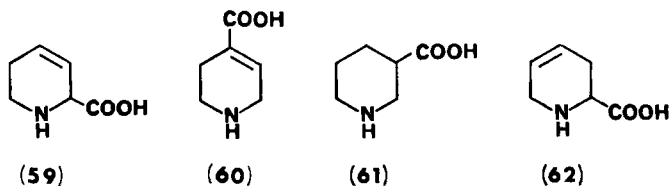
<sup>89</sup> J. Mollin and T. Nevecna, *Acta Univ. Palacki. Olomuc., Fac. Rerum Nat.* **61/65**, 31 (1980) [*CA* **95**, 6150 (1981)].

<sup>90</sup> H. Lund, *Abh. Dtsch. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.* (1), 434 (1964) [*CA* **62**, 8674 (1965)].

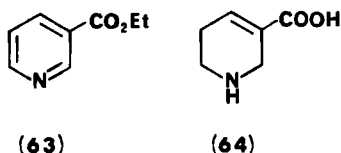
<sup>91</sup> L. N. Ferguson and A. J. Levant, *Nature (London)* **167**, 817 (1951).

<sup>92</sup> F. Sorm, *Collect. Czech. Chem. Commun.* **13**, 57 (1948).

<sup>93</sup> M. Ferles and M. Prystas, *Collect. Czech. Chem. Commun.* **24**, 3326 (1959).

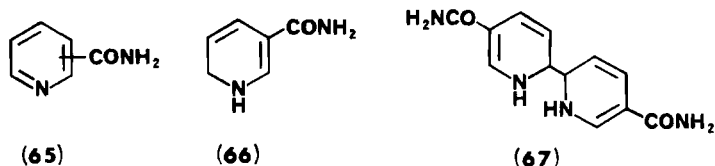


yielded the unsaturated pipecolic acid (64). Seemingly small changes in experimental technique led to different product distributions.



Lund reported the major product of the reduction of 2- and 4-acid **56** to be the aldehydes **41** and **42**, respectively<sup>94</sup>; a recent report confirmed these results in the case of 2-(**56**).<sup>95</sup> Somewhat contrary to these citations, Brown *et al.* indicated that the 2-aldehyde (**41**) was formed in low yield and that with acetate buffer the major product was carbinol **29**.<sup>96</sup> When rotating disc electrodes were used, the reduction products of 2- and 4-(**56**) were the aldehydes, but 3-(**56**) gave only catalytic hydrogen evolution.<sup>97</sup>

Polarography of the isomeric amides (**65**) was studied using the 3-isomer exclusively. At various times, dihydro products such as **66** and 6,6'-dimers (**67**) were reported.<sup>98</sup>



Reduction of 4-(**65**) gave aldehyde **42** in strong acid and carbinol **31** in acetate buffer.<sup>99</sup> In alkaline electrolyte, **31** would be further reduced to the picoline (**19**) (Scheme 19). The *N*-phenylamide gave a mixture of the carbinol

<sup>94</sup> H. Lund, *Acta Chem. Scand.* **17**, 972 (1963).

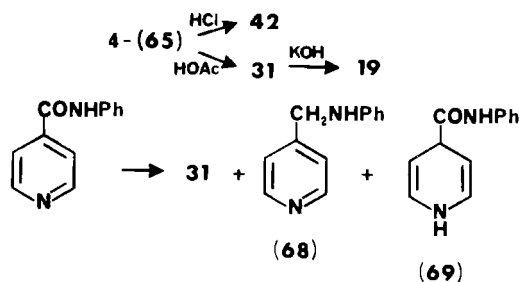
<sup>95</sup> O. Veerabhadram and K. S. Sastry, *Acta Cienc. Indica [Ser.] Chem.* **8**, 41 (1982) [*CA* **98**, 125177 (1983)].

<sup>96</sup> O. R. Brown, J. A. Harrison, and K. S. Sastry, *J. Electroanal. Chem. Interfacial Electrochem.* **58**, 387 (1975).

<sup>97</sup> M. D. Bhatti and O. R. Brown, *J. Electroanal. Chem. Interfacial Electrochem.* **68**, 85 (1976).

<sup>98</sup> K. S. V. Santhanam, C. O. Schmamel, and P. J. Elving, *Bioelectrochem. Bioenerg.* **1**, 147 (1974); D. Thevenot and R. Buve, *J. Electroanal. Chem. Interfacial Electrochem.* **40**, 197 (1972); C. O. Schmamel, K. S. V. Santhanam, and P. J. Elving, *J. Electrochem. Soc.* **121**, 345 (1974).

<sup>99</sup> H. Lund, *Acta Chem. Scand.* **17**, 2325 (1963).



SCHEME 19

(31), the *N*-phenylpicolylamine (68), and 1,4-dihydro amide (69). The other two isomers of 65 were shown to behave similarly. The amide 4-(65) could have one or both hydrogens on the amide nitrogen replaced with alkyl, benzyl, or cycloalkyl groups without altering the products.<sup>90</sup> Only when an *N*-aryl group was present did the products change, no aldehyde being observed. Iversen repeated the synthesis of the 2- and 4-aldehydes (41 and 42) on a larger scale.<sup>100</sup> The ability to form an aldehyde under conditions where it should be reduced readily was attributed to the formation of a stable hydrate, or *gem*-diol, which was resistant to further reduction. However, in Section II,D, one can note how readily hydroxyalkylpyridines are reduced, and this tends to argue against *gem*-diol stability except, perhaps, at junction potentials between aldehyde and carbinol discharge.

The radical anion initially formed on reduction of 65 could be trapped with *tert*-butyl chloride in DMF solvent.<sup>101</sup> The yields of alkylated amide were low, and the problem was traced to the rate of competitive dimerization.

Isomeric nitriles (70) are reduced to give either ring dimers, nitrile cleavage products, or picolylamines (71) (Scheme 20). The position of the polarographic wave is correlated with  $n,\pi^*$  triplet energy and the nitrile stretching frequency in the IR spectrum.<sup>10,102</sup> The mechanistic work has led to a fairly consistent scheme for rationalizing the product distribution. Thus in acid electrolytes both 2- and 4-nitriles (70) underwent a four-electron process to yield 2- and 4-amines (71),<sup>103</sup> but the isomeric 3-(70) gave a dimer identified as a dicyanobipyridine.<sup>104</sup> There are some reports of 4-(70) forming a dimer also, but the

<sup>100</sup> P. E. Iversen, *Acta Chem. Scand.* **24**, 2459 (1970).

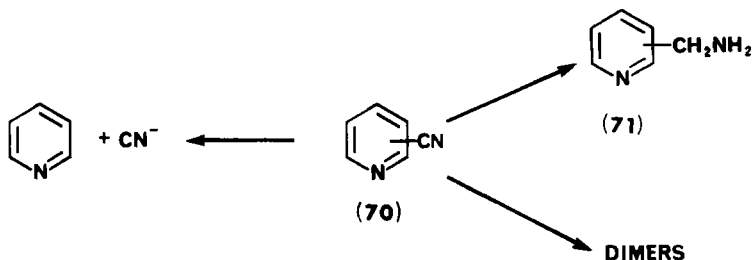
<sup>101</sup> C. Degrand, D. Jacquin, and P. L. Compagnon, *J. Chem. Res., Miniprint*, 3272 (1978).

<sup>102</sup> L. P. Krasnomolova, A. E. Lyuts, V. I. Artyukhin, O. V. Agashkin, D. Kh. Sembaev, and B. V. Suvorov, *Zh. Fiz. Khim.* **52**, 85 (1978).

<sup>103</sup> J. Volke and V. Skala, *J. Electroanal. Chem. Interfacial Electrochem.* **36**, 383 (1972); A. M. Kardos, P. Valenta, and J. Volke, *ibid.* **12**, 84 (1966); J. Volke and J. Holubek, *Collect. Czech. Chem. Commun.* **28**, 1597 (1963).

<sup>104</sup> V. A. Serazetdinova, B. V. Suvorov, and O. A. Songina, *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.* **18**, 64 (1968).



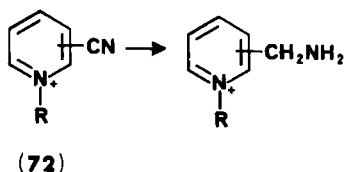


SCHEME 20

nitrile groups are lost during dimerization.<sup>105</sup> In alkaline media, nitrile cleavage predominates. The effect of ammonium ions on this reduction has also been studied.<sup>106</sup>

Contrary to the polarographic results, 3-70 can be reduced in good yield to the 3-picolylamine (71) at a palladium black on carbon cathode.<sup>107</sup> The change in orientation of 2- and 4-(70) at the electrode surface was responsible for the change in product distribution as a function of electrode potential.<sup>6,108</sup> Reduction of the nitriles (70) in liquid ammonia was also studied and the products were postulated to be dimeric under most conditions.<sup>109</sup>

The reduction of quaternary salts of the isomeric pyridinecarbonitriles (72) gave the normal four-electron product at the appropriate acidity, below pH 6 for 4-(72) and below pH 2.2 for 2-(72) (Scheme 21).<sup>110</sup> When the electrolytes were more alkaline than this, the products were dimers.



SCHEME 21

<sup>105</sup> A. Kitani, K. Iida, and K. Sasaki, *Denki Kagaku* **41**, 900 (1973).

<sup>106</sup> V. A. Serazetdinova and B. V. Suvorov, *Nov. Polyarogr., Tezisy Dokl. Vses. Soveshch. Polyarogr.*, 6th, 1975, 157 (1975); V. A. Serazetdinova, B. V. Suvorov, and O. A. Songina, *Khim. Geterotsikl. Soedin.* (3), 353 (1973).

<sup>107</sup> V. Krishnan, K. Raghupathy, and H. V. K. Udupa, *J. Electroanal. Chem. Interfacial Electrochem.* **88**, 433 (1978).

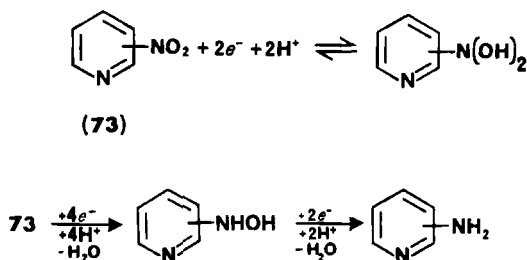
<sup>108</sup> J. Volke and A. M. Kardos, *Collect. Czech. Chem. Commun.* **33**, 2560 (1968).

<sup>109</sup> O. R. Brown and R. J. Butterfield, *Electrochim. Acta* **27**, 1647 (1982).

<sup>110</sup> I. Carelli, M. E. Cardinali, and A. Casini, *J. Electroanal. Chem. Interfacial Electrochem.* **105**, 205 (1979); M. E. Cardinali and I. Carelli, *ibid.* **125**, 477 (1981); A. Weber and J. Osteryoung, *J. Electrochem. Soc.* **129**, 2731 (1982).

H. NITRO-, AZO-, NITROSO-, HYDROXYAMINO-,  
AND AMINOPYRIDINES

Most of the work with these compounds employs voltammetry. The isomeric nitropyridines (**73**) are reduced by either a reversible two-electron or an irreversible four-electron process (Scheme 22).<sup>111</sup> The four-electron product, the hydroxylamine, can be further reduced to the amine. The *N*-oxide of 4-(**73**) was reduced to the aminopyridine (**74**) in good yield (Scheme 23).<sup>112</sup> At



SCHEME 22

intermediate stages, the product consisted of a mixture of amino-, azoxy-, and azopyridine *N*-oxides (**75**). The azo compounds resulted from the condensation of intermediate products. Nitrolutidine (**76**) was reduced to aminolutidine (**77**) (Scheme 24).<sup>113</sup> The 2-chloro-5-nitro compound (**78**) also yielded an amino compound<sup>114</sup> as did the 3-nitro precursors to pyridoxamine.<sup>115</sup> Lund and Sharma studied the reduction of nitraminopyridines.<sup>116</sup>

Even though most of the synthetic work was directed toward four- and six-electron reduction of nitro groups, voltammetry suggests that other products could result.<sup>117</sup> In one of the above examples, the first-formed nitroso compound can form azoxy "dimers," which are subsequently reduced to the azo compounds.

<sup>111</sup> A. Darchen and C. Moinet, *J.C.S. Chem. Commun.*, 487 (1976).

<sup>112</sup> J. Hranilović, D. Koruncev, and E. Gustak, *Electrochem. Technol.* **6**, 62 (1968); H. Miyazaki and T. Kubota, *Bull. Chem. Soc. Jpn.* **44**, 279 (1971); E. G. Novikov and A. G. Pozdeeva, *Zh. Prikl. Khim.* **40**, 202 (1967).

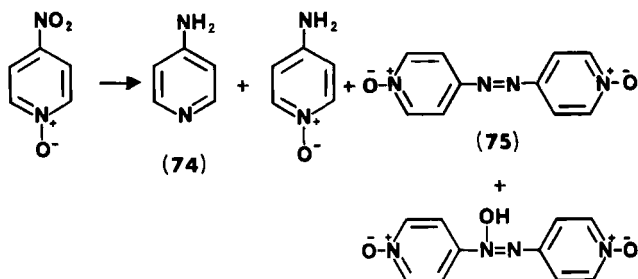
<sup>113</sup> E. Ochiai, I. Iwai, and H. Negoro, *J. Pharm. Soc. Jpn.* **61**, 230 (1941).

<sup>114</sup> A. Binz and O. Schickh, *Ber. Dtsch. Chem. Ges.* **68A**, 315 (1935).

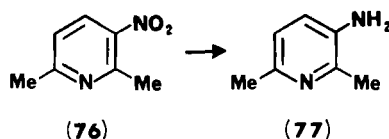
<sup>115</sup> M. Laćan, I. Tabaković, J. Hranilović, N. Bujas, and Z. Stunić, *Croat. Chem. Acta* **43**, 229 (1971); M. Laćan, I. Tabaković, J. Hranilović, Z. Vajtner, and R. Hranilović, *ibid.* **44**, 385 (1972).

<sup>116</sup> H. Lund and S. K. Sharma, *Acta Chem. Scand.* **26**, 2329 (1972).

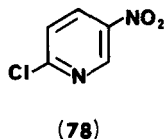
<sup>117</sup> M. Person, T. Francois-Habert, and D. Beau, *C.R. Hebd. Seances Acad. Sci., Ser. C* **279**, 379 (1974); M. Charton, R. Gawinecki, A. Kapturkiewicz, D. Rasala, and P. Tomasik, *Commun. Czech.-Pol. Colloq. Chem. Thermodyn. Phys. Org. Chem.*, 2nd, 1980, 177 (1980).



SCHEME 23



SCHEME 24



The azo *N*-oxide (75) was reduced in DMF to the dianion of azopyridine.<sup>118</sup> Electroinitiated polymerization of a 2-azopyridine gave a polymer useful for modifying electrode surfaces.<sup>119</sup> The only other reports of azopyridine electrochemistry involve voltammetry.<sup>120</sup>

Voltammetry on nitroso compounds confirmed what was already known about nitro reductions.<sup>121</sup> Aminopyridines were found to be nonreducible.<sup>122</sup> Oxime precursors of pyridoxylamine have been reduced on a synthetic scale.<sup>123</sup>

<sup>118</sup> J. L. Sadler and A. J. Bard, *J. Electrochem. Soc.* **115**, 343 (1968).

<sup>119</sup> M. Lapkowski, J. Zak, and J. W. Strojek, *J. Electroanal. Chem. Interfacial Electrochem.* **145**, 173 (1983).

<sup>120</sup> M. Herlem and G. Van Amerongen, *Anal. Lett.* **13**, 549 (1980); P. Tomasik, A. Tomczynska, A. Zakowicz, and H. Matynia, *Pol. J. Chem.* **53**, 855 (1979); P. Tomasik, A. Zakowicz, and W. Drzeniek, *Rocz. Chem.* **51**, 1399 (1977).

<sup>121</sup> S. Roffia and M. A. Raggi, *Atti Acad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* **52**, 84 (1972); S. Roffia and M. A. Raggi, *J. Electroanal. Chem. Interfacial Electrochem.* **67**, 11 (1976); S. Roffia, M. A. Raggi, and M. Ciano, *ibid.* **62**, 403 (1975).

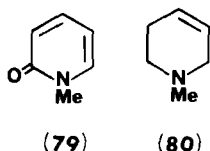
<sup>122</sup> A. G. Pozdeeva and E. G. Novikov, *Zh. Prikl. Khim.* **42**, 2626 (1969).

<sup>123</sup> O. Manousek, *Collect. Czech. Chem. Commun.* **25**, 2250 (1960).

## I. PYRIDONES

The probable orientation of 3-hydroxy-2-pyridone at the electrode surface is perpendicular with strong interaction between the metal and nitrogen of the ring.<sup>124</sup> The only voltammetry done in these systems was on a thione derivative.<sup>125</sup>

As expected, macroscale reduction gave products corresponding to those from reduction of the parent pyridine, that is, piperidine and piperidines. Electrolysis of a series of *N*-alkyl-substituted 2-pyridones, for example *N*-methyl-(79), yielded a mixture of *N*-methylpiperidine and -piperidine 80.<sup>126</sup> Reduction of the methyl ether of 2-pyridone gave piperidine only.<sup>127</sup>



## J. HALOPYRIDINES

Selective dehalogenation of halopyridines is an important industrial process for the same reason that reduction of carboxylic acids, esters, amides, and nitriles are also important. There is a dearth of selective oxidation technologies whether by conventional or electrochemical methods. Therefore, many intermediate oxidation stage products are made by overoxidation, i.e., overhalogenation, followed by selective reduction.

The mechanism of reductive dechlorination of the isomeric chloropyridines (81)<sup>128</sup> appears to be different in water-ethanol as opposed to DMF.<sup>129</sup> For other halopyridines the ease of reduction followed the expected order  $I > Br > Cl$ .<sup>130</sup>

<sup>124</sup> M. P. Soriaga and A. T. Hubbard, *J. Am. Chem. Soc.* **104**, 2735 (1982).

<sup>125</sup> R. Lejeune, J. L. Vandenbalck, G. J. Patriarche, and C. L. Lapiere, *Bull. Soc. Chim. Belg.* **90**, 663 (1981).

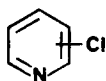
<sup>126</sup> M. Ferles and H. Hrubá, *Z. Chem.* **9**, 450 (1969).

<sup>127</sup> T. B. Graves, *J. Am. Chem. Soc.* **46**, 1460 (1924).

<sup>128</sup> J. Holubek and J. Volke, *Collect. Czech. Chem. Commun.* **27**, 680 (1962); S. G. Mairanovskii and R. G. Baisheva, *Electrokhimiya* **5**, 893 (1969); M. Maruyama and K. Murakami, *Nippon Kagaku Kaishi* (12), 2119 (1975); *ibid.* (11), 1715 (1976).

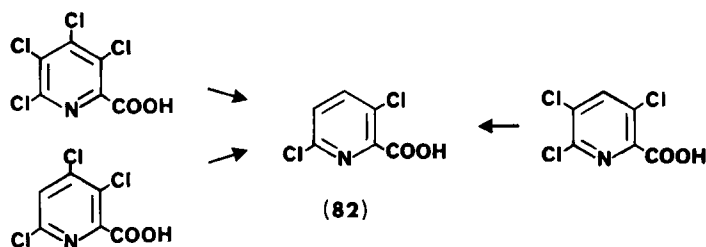
<sup>129</sup> C. P. Andrieux, C. Blocman, J.-M. Dumas-Bouchiat, and J.-M. Saveant, *J. Am. Chem. Soc.* **101**, 3431 (1979); S. Kashti and E. Kirowa-Eisner, *J. Electroanal. Chem. Interfacial Electrochem.* **103**, 119 (1979); S. Kashti-Kaplan and E. Kirowa-Eisner, *Isr. J. Chem.* **18**, 75 (1979).

<sup>130</sup> R. F. Evilia and A. J. Diefenderfer, *J. Electroanal. Chem. Interfacial Electrochem.* **22**, 407 (1969); R. F. Evilia, Ph.D. Thesis, Lehigh University, Bethlehem, Pennsylvania (1969).

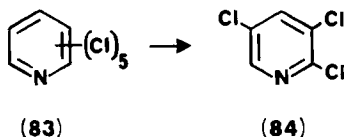


(81)

Dow Chemical has most of the patents for dehalogenation of halopyridines. For instance, 3,6-dichloropicolinic acid (**82**) was claimed as the product from dechlorination of three more highly chlorinated materials (Scheme 25).<sup>131</sup> Dechlorination of pentachloropyridine (**83**) to the trichloro

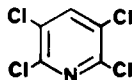


SCHEME 25



SCHEME 26

material (**84**) used a silver cathode (Scheme 26).<sup>132</sup> The pentachloro compound (**83**) was also reduced to the symmetrical tetrachloro derivative (**85**).<sup>133</sup> Selective replacement of halogens in halogenated halomethylpyridines was also disclosed.<sup>134</sup> Thus selective dechlorination of chlorinated trifluoromethylpyridines gave either monochloro (**86**) or fully dechlorinated material (**87**) (Scheme 27).<sup>135</sup>



(85)

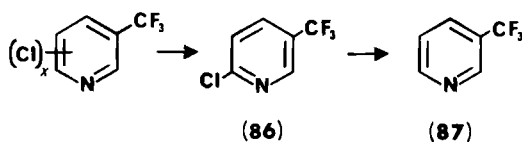
<sup>131</sup> D. Kyriacou, F. Edamura, and J. Love, U. S. Patent 4,217,185 [CA 94, 22193 (1981)]; D. K. Kyriacou, "Basics of Electroorganic Syntheses," pp. 112-117. Wiley, New York, 1981.

<sup>132</sup> D. Kyriacou, U. S. Patent 4,242,183 [CA 94, 54933 (1981)].

<sup>133</sup> V. D. Parker, U. S. Patent 3,694,332 [CA 77, 164492 (1972)].

<sup>134</sup> J. N. Seiber, U. S. Patent 3,687,827 [CA 77, 151980 (1972)].

<sup>135</sup> P. H. Gamlen, U. K. Patent 2,089,801 (1982).



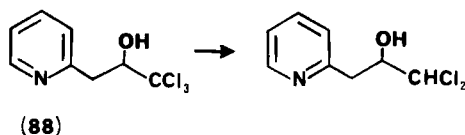
SCHEME 27

Perchlorinated vinylpyridines were reduced to pyridylacetylenes where none, one, or more halogens were also removed from the aromatic nucleus (Scheme 28).<sup>136</sup> Attempts to dehalogenate the trichloromethylcarbinol (88)

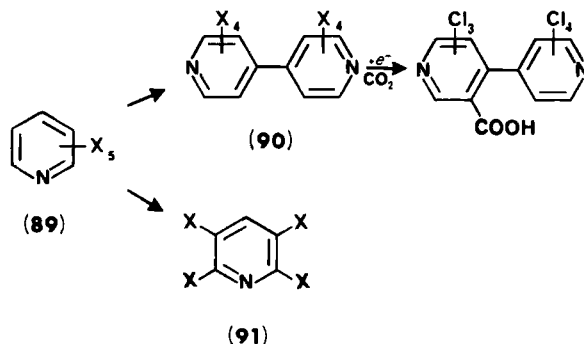


SCHEME 28

beyond the dichloromethyl compound were not successful (Scheme 29).<sup>137</sup> In DMF solvent, pentafluoropyridine (89, X = F) was reduced to the perfluorinated bipyridyl (90, X = F) (Scheme 30).<sup>138</sup> Perchlorinated bipyridyl



SCHEME 29



SCHEME 30

<sup>136</sup> J. N. Seiber and V. D. Parker, U.S. Patent 3,673,190 [CA 77, 126442 (1972)]; J. N. Seiber, *J. Org. Chem.* **36**, 2000 (1971).

<sup>137</sup> K. Brand and K. Reuter, *Ber. Dtsch. Chem. Ges. B* **72**, 1668 (1939).

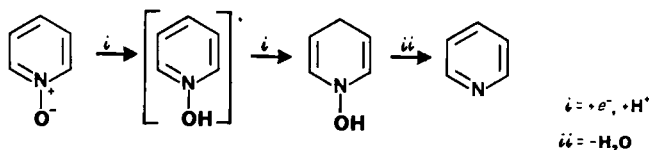
<sup>138</sup> R. D. Chambers, W. K. R. Musgrave, C. R. Sargent, and F. G. Drakesmith, *Tetrahedron* **37**, 591 (1980).

(**90**, X = Cl) was subsequently carboxylated in the 3-position. In the presence of a proton donor, the major product from reduction of **89** (X = F) was the symmetrical tetrahalo **91**. When pentachloropyridine (**89**, X = Cl) was reduced without an added proton donor, the tetrachloro **91** (X = Cl) was the major product; dimerization to bipyridyl (**90**, X = Cl) was sterically inhibited.

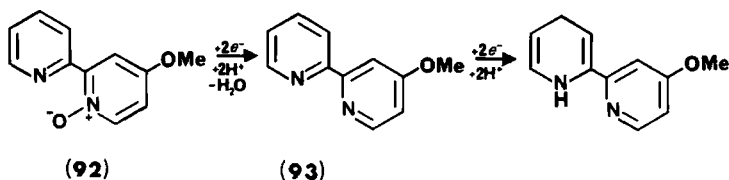
### K. N-OXIDES

A great deal of chemistry can be done on pyridine *N*-oxides because the functionality acts as a modifier of ring reactivity. In some cases, the *N*-oxide functionality needs to be removed after the transformations of interest have been done; a selective, mild reduction process would be of value.

The two-electron–two-proton reduction follows the course outlined in Scheme 31.<sup>139</sup> Macroscale reductions of the *N*-oxides of pyridine and its alkyl derivatives gave good yields of pyridine base.<sup>140</sup> Overreduction would also be expected to give piperidine and piperidine bases and one report describes such a process.<sup>141</sup> The electrolytic yields were generally good as compared to other reduction methods. The substituted bipyridine *N*-oxide (**92**) gave the deoxygenated product (**93**) initially, followed by reduction of the unsubstituted ring to a dihydrobipyridine; this last step has not been supported by macroscale synthesis (Scheme 32).<sup>142</sup> Substituent effects on the reduction have



SCHEME 31



SCHEME 32

<sup>139</sup> G. Anthoine, J. Nasielski, E. Vander Donckt, and N. Vanlauten, *Bull. Soc. Chim. Belg.* **76**, 230 (1967).

<sup>140</sup> L. Horner and H. Röder, *Chem. Ber.* **101**, 4179 (1968).

<sup>141</sup> M. Jankovsky and M. Ferles, *Collect. Czech. Chem. Commun.* **35**, 2802 (1970).

<sup>142</sup> S. S. Katiyar, M. Lalithambika, and R. P. Shukla, *Bull. Chem. Soc. Jpn.* **45**, 685 (1972).

been studied.<sup>143</sup> Voltammetry reports suggest that reducible substituents in the 2- or 4-position are reduced concurrently during deoxygenation.<sup>9,111,113,117,144</sup> This, of course, limits the selectivity of the process.

## L. PYRIDINIUM SALTS

One-third of all pyridine electrochemical citations deal with the electrolysis of quaternary salts of pyridines; two out of five cathodic reports are concerned with them. Moreover, the products of reduction and the salts themselves are commercially valuable. A whole class of biochemical transformations depends on the reactivity of pyridinium ions. Agricultural products are also derived from these salts, and the value of bipyridinium herbicides is directly linked to their redox chemistry.

These electrolyses provide a good example of the selectivity that can be achieved. As a group, they are easy to reduce and the functionality on nitrogen does not normally participate in the reduction process. In many cases, the radicals and radical ions derived from the quaternary salts have some stability, sometimes with half-lives on the order of minutes or hours.

Initial electron transfer to a pyridinium ion forms a neutral radical (**94**); the mechanistic pathways open for reduction should be (and are) different from those for neutral pyridines where the initial electron transfer forms a radical anion (see Scheme 1). Radical **94** can dimerize, abstract hydrogen, transfer an electron to another substrate, undergo a crossed hydrocoupling, or be further reduced to the anion **95** (Scheme 33). Protonation or hydrocoupling reactions can ensue from **95**. Most of these reaction pathways seem to have been experimentally observed.

A study of the initially formed **94** used acetonitrile solvent.<sup>145</sup> Rapid chemical follow-up steps were proposed. Reduction in aqueous solution was shown to proceed along similar lines.<sup>146</sup> The energies of Hückel molecular orbitals for alkylpyridinium ions indicated that no correlation exists between reduction potential and the quaternary nitrogen electron density.<sup>147</sup> EPR spectra of the radicals (**94**) were analyzed.<sup>148</sup>

<sup>143</sup> T. Kubota and H. Miyazaki, *Bull. Chem. Soc. Jpn.* **39**, 2057 (1966).

<sup>144</sup> A. F. Krivis and E. S. Gazda, *Anal. Chem.* **41**, 212 (1969); E. Laviron, R. Gavasso, and M. Pay, *Talanta* **17**, 747 (1970); R. W. Janssen, Ph.D. Thesis, Rutgers University, New Brunswick, New Jersey (1969).

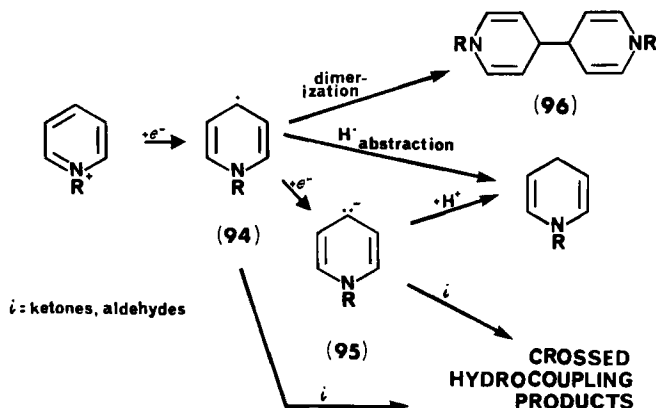
<sup>145</sup> R. Raghavan and R. T. Iwamoto, *J. Electroanal. Chem. Interfacial Electrochem.* **92**, 101 (1978); R. Raghavan, Ph.D. Thesis, University of Kansas, Lawrence (1975).

<sup>146</sup> J. G. Gaudiello, D. Larkin, J. D. Rawn, J. J. Sosnowski, E. E. Bancroft, and H. N. Blount, *J. Electroanal. Chem. Interfacial Electrochem.* **131**, 203 (1982).

<sup>147</sup> P. Nagy, I. Goerbe, and A. Szurkos, *Rev. Roum. Chim.* **17**, 1115 (1972).

<sup>148</sup> D. Guerin-Ouler, C. Nicollin, C. Sieiro, and C. Lamy, *Mol. Phys.* **34**, 161 (1977).





SCHEME 33

Reduction of *N*-alkylpyridinium ions leads to dimerization even in aqueous solutions as long as strong acids are absent. In the presence of strong acids, the reduction products are normally piperideines and piperidines. For example, the reduction products and product ratios of the isomeric lutidine *N*-methyl quaternary salts are almost identical to those shown in Scheme 6, except now there is an *N*-methyl group on the reduced bases.<sup>46</sup> The same was true for the methyl quaternized picoline (**16**).<sup>149</sup> Similarly, reduction of the *N*-methyl ion of symmetrical collidine gave nearly the same product distribution as the free base, again with an *N*-methyl group on the reduced bases (see **22–25**).<sup>48</sup> One report claims the isolation of bipiperidines from such a reduction, the tetrahydrobipyridine being an intermediate.<sup>150</sup> Quaternary salts of pyridylcarbinols and ketones gave similar types of products.<sup>151</sup>

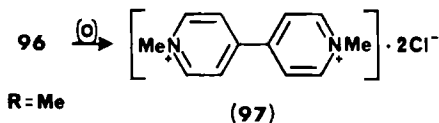
The dimerization of **94** to give tetrahydrobipyridines (**96**) is of commercial interest because **96** can be oxidized to the herbicide Paraquat (**97**) (Scheme 34).<sup>152</sup> Most of this electrolytic work stems from a report by Emmert,

<sup>149</sup> M. Ferles and J. Holik, *Collect. Czech. Chem. Commun.* **31**, 2416 (1966).

<sup>150</sup> E. Ochiai and H. Kataoka, *J. Pharm. Soc. Jpn.* **62**, 241 (1942); E. Ochiai and N. Kawagoye, *ibid.*, 313.

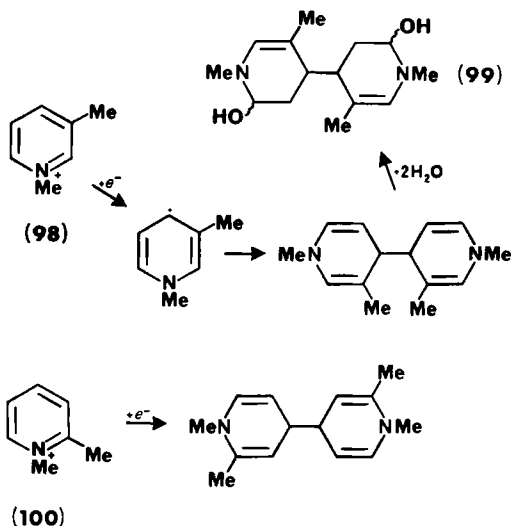
<sup>151</sup> M. Ferles, O. Kocian, M. Lebl, J. Lovy, S. Radl, A. Silhankova, and P. Stern, *Collect. Czech. Chem. Commun.* **41**, 598 (1976); M. Ferles and A. Attia, *ibid.* **38**, 2747 (1973).

<sup>152</sup> T. Misumi, S. Furuhashi, and M. Shiga, U.S. Patent 4,176,020 [CA **90**, 22828 (1979)]; J. E. Colchester and J. H. Entwisle, U.S. Patent 3,478,042 [CA **72**, 31627 (1970)]; J. E. Colchester and J. H. Entwisle, U.S. Patent 3,717,646 [CA **78**, 147811 (1973)]; S. G. Mairanovskii, V. P. Gul'tyai, A. P. Churilina, N. K. Lisitsina, and S. Hillers, Russian Patent 497,293 [CA **84**, 135486 (1976)]; A. P. Tomilov, Yu. D. Smirnov, O. N. Dymont, L. I. Kostikin, V. K. Promonenkov, V. D. Simonov, and Yu. A. Kondrat'ev, Russian Patent 763,337 [CA **94**, 174889 (1981)]; M. Kato, *Kagaku Zokan (Kyoto)* (**86**), 147 (1980) [CA **94**, 173713 (1981)]; J. Volke, *Collect. Czech. Chem. Commun.* **33**, 3044 (1968).



SCHEME 34

and the process patents are improvements on this disclosed process.<sup>153</sup> Bird and Kuhn<sup>154</sup> reviewed the electrochemistry of quaternized bipyridines. The use of these materials as electron transfer agents or mediators in electrochemical reactions is becoming more prominent, and this application should be advantageous, both when used as a homogeneous mediator and as a stationary phase on electrode surfaces.<sup>155</sup> The dimerization of picoline quaternary salt **98** was studied by voltammetry, and the dimer was postulated to undergo hydration to **99**,<sup>156</sup> but the isomeric salt (**100**) seemed to be reduced normally (Scheme 35).<sup>157</sup> There was no isolation of **99** and this reaction must be regarded as anomalous until verified.



SCHEME 35

<sup>153</sup> B. Emmert, *Ber. Dtsch. Chem. Ges.* **42**, 1997 (1909).

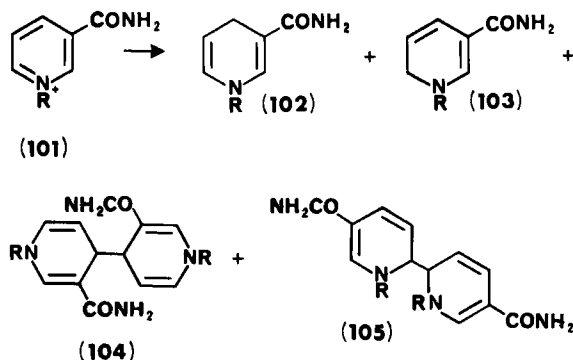
<sup>154</sup> C. L. Bird and A. T. Kuhn, *Chem. Soc. Rev.* **10**, 49 (1981); see also A. Deronzier, B. Galland, and M. Vieira, *Electrochim. Acta* **28**, 805 (1983).

<sup>155</sup> R. T. Salmon and F. M. Hawkrige, *J. Electroanal. Chem. Interfacial Electrochem.* **112**, 253 (1980); A. Deronzier, B. Galland, and M. Vieira, *Nouv. J. Chim.* **6**, 97 (1982); S. Hünig, J. Gross, and W. Schenk, *Liebigs Ann. Chem.*, 324 (1973).

<sup>156</sup> M. G. Bonicelli, M. E. Cardinali, and I. Carelli, *J. Electroanal. Chem. Interfacial Electrochem.* **131**, 345 (1982).

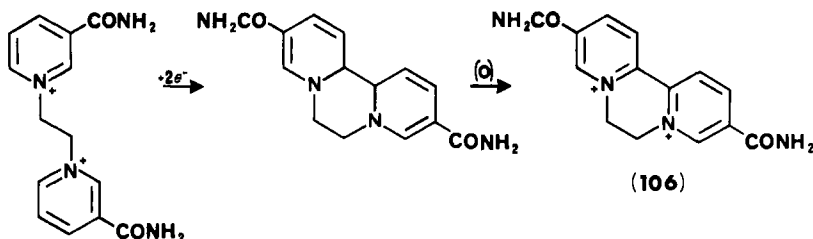
<sup>157</sup> Japanese Kokai Tokyo Koho Patent 81/112,488 [*CA* **96**, 59966 (1982)].

The electrochemistry of N-substituted nicotinamides (**101**) dominates the reports on ring-substituted pyridinium ions. There is also some controversy about the products of reduction. Elving *et al.* have reviewed this area up to about 1975.<sup>158</sup> Apparently there is little doubt that a dihydro product, either **102** or **103**, and dimer, either **104** or **105**, are formed (Scheme 36). The latest



SCHEME 36

reports make it clear that 1,4-dihydro-(**102**) and the 4,4'-dimer (**104**) are the preferred products under most circumstances.<sup>159</sup> Reports on the structure of the major dimer prior to about 1978 relied heavily on UV spectroscopy; these reports are not correct when indicating the 6,6'-dimer (**105**) as the major dimeric product. However, there are conditions under which the 6,6'-dimeric products may be formed, such as when the two N-substituents are part of the same carbon chain (Scheme 37).<sup>160</sup> Interestingly, the 6,6'-dimer in this case



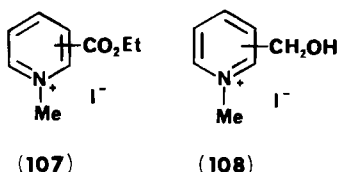
SCHEME 37

<sup>158</sup> P. J. Elving, C. O. Schmakel, and K. S. V. Santhanam, *CRC Crit. Rev. Anal. Chem.* **6**, 1 (1976); C. O. Schmakel, K. S. V. Santhanam, and P. J. Elving, *J. Am. Chem. Soc.* **97**, 5083 (1975).

<sup>159</sup> V. Carelli, F. Liberatore, A. Casini, R. Mondelli, A. Arnone, I. Carelli, G. Rotilio, and I. Mavelli, *Bioorg. Chem.* **9**, 342 (1980); J. Hermolin, E. Kirowa-Eisner, and E. M. Kosower, *J. Am. Chem. Soc.* **103**, 1591 (1981).

<sup>160</sup> D. J. McClemens, A. K. Garrison, and A. L. Underwood, *J. Org. Chem.* **34**, 1867 (1969).

could be oxidized with oxygen to give the bipyridinium (106); the reports on the 4,4'-dimer (104) are all consistent in suggesting that oxidation by air or electrolysis reverts the dimer to monomer pyridinium (101). The ratio of dihydro to dimer products was also sensitive to the concentration of 101 in solution, dimers being favored at high concentrations, as expected.<sup>161</sup> These results represent yet another example of the need to study product ratios as a function of experimental parameters, where the effect of each variable can be studied independently.



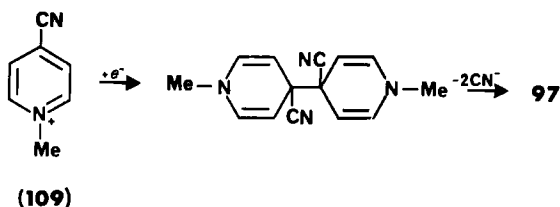
As a general rule, when the electrolyte is acidic, reduction of pyridinium ions having a reducible ring substituent leads to reduction of the substituents. For instance, reduction of the isomeric ester quaternary salts (107) in acid yields the carbinols (108); the isomeric cyano-substituted pyridinium ions behave similarly, giving the picolylamines.<sup>110</sup> The 2- and 4-(107) isomers give the highest yield of carbinol, and 3-(107) has the most stable neutral radical.<sup>162</sup> When the pH is raised, dimers become the primary products; again, there is a certain amount of doubt about where the rings are coupled.<sup>110,163</sup> Before these products can be identified with certainty, analytical methods will have to be developed to allow an unambiguous determination of all the possible positions of coupling to form a dimer. The development of such methods is hampered by the large number of unique dimers that can be formed from each pyridinium salt. For instance, six dimers can be formed from a ring-unsubstituted pyridinium ion; when a single ring substituent is present, there are ten possible dimers. As a curious sidelight, reduction of the 4-cyanopyridinium salt (109) in nonaqueous media gave Paraquat (97) (Scheme 38).<sup>164</sup> This result is in accord with what is known about chemically induced dimerization of pyridinium ions to form 97. On the other hand, the radical

<sup>161</sup> F. Micheletti Moracci, S. Tartorella, B. Di Rienzo, F. Liberatore, and I. Carelli, *Ann. Chim. (Rome)* **71**, 499 (1981).

<sup>162</sup> O. R. Brown, R. McIntyre, and P. L. H. Miller, *J. Electroanal. Chem. Interfacial Electrochem.* **110**, 247 (1980); see also S. Kashti-Kaplan, J. Hermolin, and E. Kirowa-Eisner, *J. Electrochem. Soc.* **128**, 802 (1981).

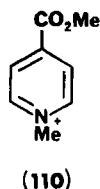
<sup>163</sup> J. Hermolin, M. Levin, Y. Ikegami, M. Sawayanagi, and E. M. Kosower, *J. Am. Chem. Soc.* **103**, 4795 (1981); H. Kinoshita, M. Uehara, and J. Nakaya, *Bull. Univ. Osaka Prefect., Ser. A* **29**, 157 (1980).

<sup>164</sup> A. Webber and J. Osteryoung, *J. Electrochem. Soc.* **129**, 2731 (1982).



SCHEME 38

formed from ester **110** was found to be quite stable, i.e., distillable.<sup>163</sup> Also, as was seen in the case of the amide-substituted pyridinium ions (Scheme 37), joining two pyridine rings through a methylene chain alters the reductive process.<sup>165</sup> Studies on this system clearly show the intricate mechanistic details that should be considered when studying electrochemical transformations. The stability of radicals formed from 4-substituted pyridinium ions has been exploited to prepare materials suitable for electrochromic displays.<sup>166</sup> Radical ions of **97** serve the same purpose.



Ferles *et al.* have studied the crossed hydrocoupling of acetone and cyclopentanone with pyridinium salts.<sup>167</sup> The products were similar to those found for hydrocoupling of ketones with the pyridine free bases except for the *N*-alkyl group. In the case of cyclopentanone, the tertiary alcohol product eliminated water in some cases to form an olefin.

### M. DIHYDROPYRIDINES

The only studies on dihydropyridines are voltammetric experiments in which the effect of substituents in the 3- and 5-positions of 1,4-dihydro-

<sup>165</sup> J. Hermolin, S. Kashti-Kaplan, and E. Kirowa-Eisner, *J. Electroanal. Chem. Interfacial Electrochem.* **123**, 307 (1981).

<sup>166</sup> N. Yoshiike, S. Kondo, and M. Fukai, *J. Electrochem. Soc.* **127**, 1496 (1980).

<sup>167</sup> M. Ferles, M. Lebl, P. Stern, and P. Trska, *Collect. Czech. Chem. Commun.* **40**, 2183 (1975).

pyridine was examined.<sup>168</sup> For instance, when the 3,5-substituents were —COMe or —CN, the reduction wave was most anodic, but when they were —COEt, no reduction was observed. Evidence was presented to support the hypothesis that the ring was reduced and not the substituent.

### III. Anodic Reactions

Less than 10% of the reports on pyridine electrochemistry deal with anodic reactions. The mechanisms of these reactions are rarely known and, as a result, yields or current efficiencies have not always been optimized. Many of the anodic reactions were studied in beaker cells, which are simply not good models for modern flow cells; moreover, uncontrolled power supplies were often used. Consequently, anode overpolarization caused ring degradation in many cases.

Oxidative reactions of pyridines are commercially more interesting than reductive ones because catalytic hydrogenation of pyridines is a generally useful method, whereas catalytic oxidation is not. In contrast, anodic oxidation of pyridines is widely applicable and can replace methods that use expensive oxidants such as permanganate salts or chromic oxide. Consider, as an example, oxidation of a methylpyridine to produce 1 kg of the pyridinecarboxylic acid; this process would consume about \$3 worth of potassium permanganate at 100% efficiency and would produce 0.7 kg of by-product MnO<sub>2</sub> for disposal or recycle. The same anodic reaction would consume only \$0.30 of electrical power (for oxidation) and would not produce a significant amount of material for disposal.

The greatest amount of work has been done on the oxidation of alkylpyridines and pyridine itself. However, this reported synthesis technology was neither modern nor necessarily optimum.

Very little work has been done on selectivity in anodic reactions of pyridines. Selective methoxylation and acetoxylation are known for alkylbenzenes, but such reactions have not been reported for alkylpyridines. Also, reports on the oxidation of pyridines having aldehyde, ketone, halogen, hydroxyalkyl, or aminoalkyl functionalities are sparse.

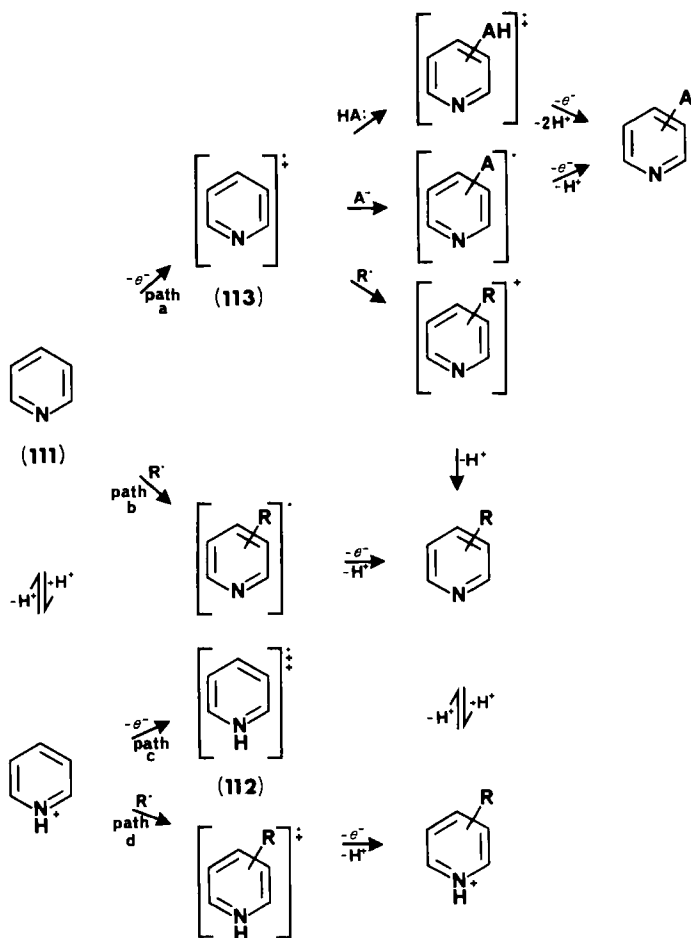
Because the merits of anodic reactions of pyridines have yet to be fully realized, the discussion will include reactions that have low reported yields but are nevertheless of industrial interest. This will be especially important for the

<sup>168</sup> J. Kuthan, J. Volke, V. Volkeova, and V. Simonek, *Collect. Czech. Chem. Commun.* **39**, 3438 (1974); V. Kadis, G. Duburs, J. Stradins, and J. Uldrikis, *Khim. Geterotsikl. Soedin.* (5), 641 (1978).

anodic oxidations of pyridine itself. These methods are sometimes an excellent way to obtain functionalized pyridines in a single step, which would otherwise require a multistep conventional process.

### A. PYRIDINE

Pyridine (**111**) oxidation can occur by four different routes (Scheme 39); paths a and c are direct electron transfers from **111** and the pyridinium cation, respectively. The other two pathways represent corresponding indirect

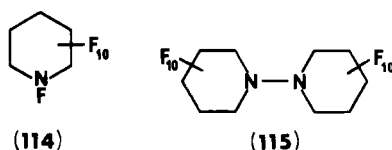


SCHEME 39

oxidation by electrogenerated radicals. Radical substitution is shown in paths b and d, but the radical species could just as well have been a metal ion, in which case only indirect electron transfer, and not substitution, would have occurred. Of course, path c is unlikely because the radical dication **112** has an unfavorable charge density. The other three pathways appear to have been observed. However, there is little direct evidence bearing on the mechanistic pathway taken in any individual reaction.

Anodic oxidation of **111** can lead to ring degradation, and there are reports of processes giving mainly oxidized fragments.<sup>169</sup> It is common in the older literature to see reports of this degradation occurring concurrently with a more selective oxidation. The lack of controlled power supplies would appear to have been part of the problem, although not all of it. The relative extent of ring degradation can be assessed by examining the anolyte or its vent gases for low-molecular-weight, highly oxidized fragments. The ability to functionalize **111** directly justifies closer scrutiny of these anodic reactions despite the experimental difficulties involved. In addition, working out the mechanistic pathways involved would seem to be conducive to realizing the full merit of these anodic transformations.

Fluorination of **111** appears to be an example of radical ion **113** being trapped by a nucleophile (path a of Scheme 39). Perfluorinated products **114** and **115** are formed in low yield using the Simmons process, the major



products being perfluorinated fragments.<sup>170,170a</sup> In some cases, the perfluorinated fragments retained the full carbon backbone, perfluoropentane being formed from pyridine, but smaller carbon fragments were also seen. Yeager, Olah, and Huba observed that when the junction potential is kept low, 2-fluoropyridine (**116**) is made, but again in low yield (Scheme 40).<sup>171</sup> They proposed that the 2-pyridylpyridinium cation (**117**) was formed during the

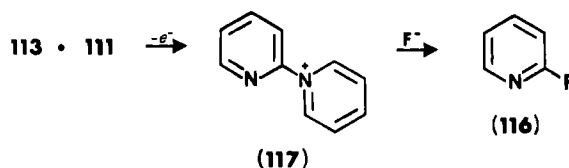
<sup>169</sup> E. P. Rivkind, K. G. Mityanina, E. I. Grinblat, and E. K. Derbysheva, *Vopr. Tekhnol. Ulavlivaniya Pererab. Prod. Koksovaniya* (2), 102 (1974) [*CA* **82**, 49208 (1975)]; M. Yokoyama and K. Yamamoto, *Bull. Chem. Soc. Jpn.* **7**, 28 (1932).

<sup>170</sup> T. C. Simmons, F. W. Hoffmann, R. B. Beck, H. V. Holler, T. Katz, R. J. Koshar, E. R. Larsen, J. E. Mulvaney, K. E. Paulson, F. E. Rogers, B. Singleton, and R. E. Sparks, *J. Am. Chem. Soc.* **79**, 3429 (1957); E. A. Kauck and J. H. Simmons, U. S. Patent 2,616,927 (1952); J. H. Simmons, U. S. Patents 2,490,098 (1949) and 2,519,983 (1950); R. E. Banks, A. E. Ginsberg, and R. N. Haszeldine, *J. Chem. Soc.*, 1740 (1961).

<sup>170a</sup> V. J. Davis, R. N. Haszeldine, and A. E. Tipping, *J.C.S. Perkin I*, 1263 (1975).

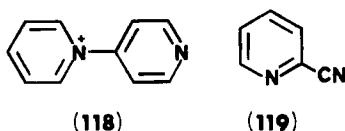
<sup>171</sup> F. Huba, E. B. Yeager, and G. A. Olah, *Electrochim. Acta* **24**, 489 (1979).





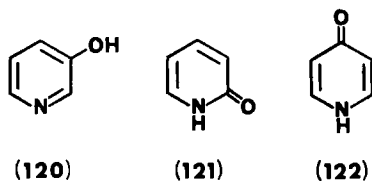
SCHEME 40

fluorination, although it is not clear whether cation 117 reacted further with fluoride ion to give the fluoropyridine or whether 116 arose only from the radical cation. There is some evidence that cation 117 may play a role in other pyridine oxidations. Persulfate oxidation gave the same cation.<sup>172</sup> On the other hand, the formation of 117 here should be contrasted to the formation of the isomeric 4-cation 118 during thionyl chloride oxidation of 111. The utility



of these cations is due to the ease of displacement of the pyridinium moiety by a variety of nucleophiles. Hence an entry to a large number of 2-substituted pyridines might be gained through the 2-cation 117. A low yield of 2-cyanopyridine (119) was claimed for the controlled potential electrolysis of 111 in the presence of a tetraalkylammonium cyanide;<sup>173</sup> however, examination of the referenced paper does not disclose this particular reaction.<sup>173a</sup> Anodic oxidation of 111 in aqueous sulfuric acid gave products on alkali cleavage that were suggestive of the formation of 2-cation 117.<sup>172</sup> 2-Cyanopyridine (119) was made in a plasma discharge with 111 in the presence of acetonitrile in good yield, but low conversion.<sup>174</sup>

Hydroxylation of 111 gave mostly 3-hydroxypyridine (120) and lesser amounts of the isomeric tautomers 2- (121) and 4-pyridone (122).<sup>175</sup> Because the oxidation was done under strongly acidic conditions, this appears to be an



<sup>172</sup> P. Baumgarten and E. Dammann, *Ber. Dtsch. Chem. Ges. B* **66**, 1633 (1933).

<sup>173</sup> R. F. Nelson, *Tech. Chem. (N.Y.)* **5**, Part 2, 323 (1975).

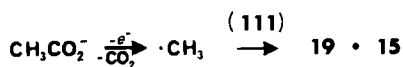
<sup>173a</sup> S. Andreades and E. W. Zahnow, *J. Am. Chem. Soc.* **91**, 4181 (1969).

<sup>174</sup> L. L. Miller and A. B. Szabo, *J. Org. Chem.* **44**, 1670 (1979).

<sup>175</sup> J. Wellmann and E. Steckhan, *Chem. Ber.* **110**, 3561 (1977).

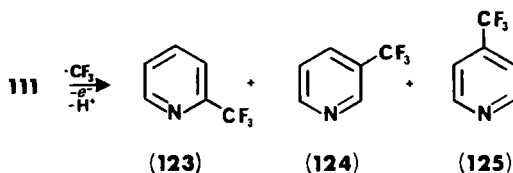
example of a path d oxidation (Scheme 39). Best results were obtained when the products could be extracted continuously from the oxidizing medium; this could not be done with the hydroxypyridines, and this seems to be the cause of the poor yield.

Pyridine was methylated under acidic conditions using acetate ion as a source of methyl radicals (Scheme 41).<sup>176</sup> Trapping efficiency was poor. Only 4- (19) and 2-picoline (15) were formed, and there was no 3-picoline (16), which confirmed an earlier report. 2-Picoline (15) was favored when anolyte acidity was high, suggesting that two separate pathways of Scheme 39 may have been operative.



SCHEME 41

Trifluoromethylation of 111 was done under similar conditions with trifluoroacetate ion as the radical source. Efficiency and selectivity were lower than with methylation, with all three isomers (123–125) being formed (Scheme 42). Unlike methylation, the 3-isomer (124) was favored when anolyte acidity was high. This difference in selectivity can be rationalized in terms of paths b and d (Scheme 39). The increased electrophilicity of the radical  $\cdot\text{CF}_3$  compared to  $\cdot\text{CH}_3$  would favor 3-substitution when the concentration of pyridinium ion was high. More mechanistic work needs to be done in order to identify the role of specific intermediates and to increase trapping efficiency. Diacyl peroxide decomposition in the presence of 111 is known to give good yields of alkylpyridines, so there is adequate reason to suspect that anodic generation under the right conditions could give good yields of substituted pyridines.

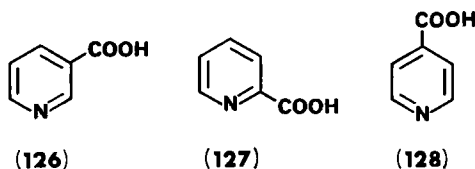


SCHEME 42

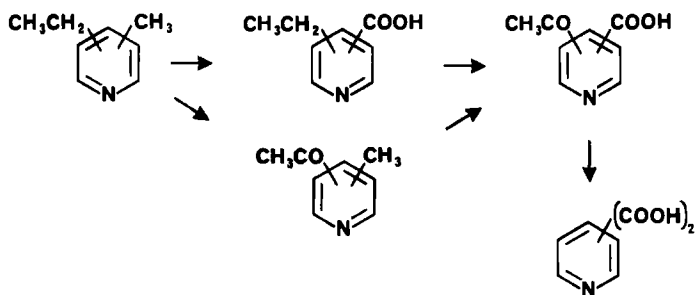
## B. ALKYL PYRIDINES

Anodic oxidation of alkylpyridines to pyridinecarboxylic acids is an old but viable synthetic procedure, usually giving the desired product in reasonable yield. In contrast to catalytic air oxidation, which works best for making

<sup>176</sup> J. H. P. Utley and R. J. Holman, *Electrochim. Acta* 21, 987 (1976).



nicotinic acid (126), both picolinic (127) and isonicotinic acids (128) and their derivatives were made by electrolysis in good yield.<sup>177-197</sup> The most-often reported technique was to use a  $\text{PbO}_2$  anode with an aqueous sulfuric acid electrolyte. Polyalkylpyridines or benzo-fused pyridines were oxidized to polycarboxylic acids.<sup>198-205</sup> Selectivity in the oxidation of polyalkylpyridines has been observed and there is reason to believe that some specific products can be made in modest yield.<sup>206</sup> Selectivity can be realized by fully oxidizing one alkyl group in preference to another or by partially oxidizing one of the alkyl groups (Scheme 43). Both of these types of partial oxidation were



SCHEME 43

<sup>177</sup> M. Yokoyama, *Bull. Chem. Soc. Jpn.* **7**, 69 (1932).

<sup>178</sup> E. Ochiai and S. Okuda, *J. Pharm. Soc. Jpn.* **70**, 156 (1950).

<sup>179</sup> H. Sagae, M. Fijihara, H. Lund, and T. Osa, *Heterocycles* **13**, 321 (1979).

<sup>180</sup> S. S. Kruglikov and V. G. Khomyakov, *Tr.—Mosk. Khim.-Tekhnol. Inst. im. D. I. Mendeleeva* (32), 194 (1961) [*CA* **57**, 16542 (1962)].

<sup>181</sup> E. Blasiak, L. Piszczek, and A. Tramer, *Chem. Stosow., Ser. A* **12**, 309 (1968).

<sup>182</sup> V. G. Khomyakov and S. S. Kruglikov, *Tr.—Mosk. Khim.-Tekhnol. Inst. im. D. I. Mendeleeva* (25), 178 (1957) [*CA* **52**, 14603 (1958)].

<sup>183</sup> M. Kulka, *J. Am. Chem. Soc.* **68**, 2472 (1946).

<sup>184</sup> V. G. Khomyakov, S. S. Kruglikov, and V. M. Berezovakii, *Zh. Obshch. Khim.* **28**, 2898 (1958) [*CA* **53**, 5916 (1959)].

<sup>185</sup> V. G. Khomyakov, S. S. Kruglikov, and N. A. Izgaryshev, *Dokl. Akad. Nauk SSSR* **115**, 557 (1957).

<sup>186</sup> F. Frichter and H. Stenzl, *Helv. Chim. Acta* **19**, 1171 (1936).

<sup>187</sup> M. Yokoyama, *Bull. Chem. Soc. Jpn.* **7**, 103 (1932).

<sup>188</sup> B. Lovreček, *Rad. Jugosl. Akad. Znanosti Umjetnosti* **296**, 65 (1953) [*CA* **48**, 6882 (1954)].

<sup>189</sup> V. V. Tsodikov, L. D. Borkhi, V. G. Brudz, N. E. Khomutov, and V. G. Khomyakov, *Khim. Geterotsikl. Soedin.* (1), 112 (1967).

reported. Stopping the oxidation at the carbinol stage is more difficult than stopping at the carbonyl stage. The commercial utility of pyridylcarbinols and pyridyl ketones justifies a more thorough investigation. Much of the nonselective synthetic work to date is fairly old, and modern synthetic methodology could improve the results significantly.

Picolinic acid (**127**) was prepared from 2-picoline (**15**) in good yield but with evidence of some ring degradation.<sup>177</sup> Acetic acid resulted from ring oxidation before the methyl group was converted. Acidic anolytes gave superior yields compared to neutral or basic anolytes.<sup>178</sup> When electrogenerated superoxide ion was used as the oxidant, no products corresponding to partial oxidation were found.<sup>179</sup>

Nicotinic acid (**126**) has been made from a variety of starting materials, most often 3-picoline (**16**)<sup>180-185</sup> but also from nicotine (**129**),<sup>186-188</sup> quinoline (**130**), or 8-hydroxyquinoline (**131**).<sup>191</sup> Again the methodology was mostly old and the synthetic cells were beaker type with ceramic dividers. The yields of the 3-acid **126** were almost as high using a practical grade picoline (93% purity) as when a much higher purity material was used. This would be important for commercial production because separating 3-picoline (**16**) from 4-picoline (**19**) by physical means is difficult. A PbO<sub>2</sub> anode was usually used but Pt was reported to work also; in the latter case, picoline was absorbed on the electrode

<sup>190</sup> V. G. Khomyakov, N. A. Kzbanovskii, and L. D. Borkhi, *Tr., Vses. Nauchno-Issled. Inst. Khim. Reakt. Osobo Chist. Khim. Veshchestv* (**29**), 304 (1966) [*CA* **67**, 116796 (1967)].

<sup>191</sup> L. D. Borkhi and V. G. Khomyakov, *Khim. Geterotsikl. Soedin.* (**1**), 167 (1967).

<sup>192</sup> J. Alamelu, K. S. Lalitha, K. Radhakrishnamurthi, S. Chidambaram, M. S. V. Pathy, and H. V. K. Udupa, *Trans. SAEST* **6**, 97 (1971).

<sup>193</sup> A. Ito and K. Kawada, *Annu. Rep. Takamine Lab.* **5**, 14 (1953).

<sup>194</sup> T. Mutavchiev and A. Marinov, *God. Vissh. Khim.—Tekhnol. Inst., Burgas, Bulg.* **2**, 193 (1956) [*CA* **52**, 11631 (1958)].

<sup>195</sup> N. Nankov and L. Yankov, *Electrokhimiya* **7**, 1865 (1971).

<sup>196</sup> L. D. Borkhi, V. G. Khomyakov, and I. G. Yakimchuk, *Tr., Vses. Nauchno-Issled. Inst. Khim. Reakt. Osobo Chist. Khim. Veshchestv* (**32**), 122 (1970).

<sup>197</sup> J. C. Cochran and W. F. Little, *J. Org. Chem.* **26**, 808 (1961).

<sup>198</sup> J. B. Conn and J. van de Kamp, U.S. Patent 2,453,701 (1948).

<sup>199</sup> J. B. Conn, U.S. Patent 2,512,483 (1950).

<sup>200</sup> V. G. Khomyakov and L. D. Borkhi, *Tr., Vses. Nauchno-Issled. Inst. Khim. Reakt. Osobo Chist. Khim. Veshchestv.* (**29**), 226 (1966).

<sup>201</sup> M. Yokoyama and K. Yamamoto, *Bull. Chem. Soc. Jpn.* **18**, 121 (1943).

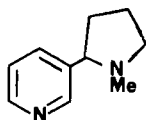
<sup>202</sup> V. G. Khomyakov, N. G. Bakhchisarait's'yan, M. Ya. Fioshin, S. S. Kruglikov, and L. I. Kazakova, *Tr.—Mosk. Khim.-Tekhnol. Inst. im. D. I. Mendeleeva* (**32**), 249 (1961) [*CA* **57**, 1974 (1962)].

<sup>203</sup> L. D. Borkhi, *Khim. Geterotsikl. Soedin.* (**10**), 1362 (1970).

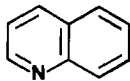
<sup>204</sup> L. D. Borkhi and V. G. Khomyakov, U.S.S.R. Patent 187,024 (1966) [*CA* **67**, 17395 (1967)].

<sup>205</sup> V. G. Khomyakov, S. S. Kruglikov, and L. I. Kazakova, *Tr.—Mosk. Khim.-Tekhnol. Inst. im. D. I. Mendeleeva* (**32**), 189 (1961) [*CA* **57**, 15065 (1962)].

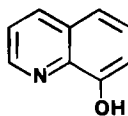
<sup>206</sup> J. Toomey, U.S. Patent applied for.



(129)



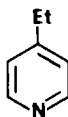
(130)



(131)

surface.<sup>182,185</sup> Addition of chromium or manganese salts, which could have acted as indirect oxidizing agents was not useful. Intermediate oxidation products were seen during the oxidation of nicotine (129).<sup>187</sup> An indirect oxidation of 129, using a basic anolyte with a manganese salt mediator, led to very good yields of 3-acid 126.<sup>188</sup> Such an indirect process would be of commercial value if the procedure were applicable to other alkylpyridines. A vanadium cation mediator was successful for the oxidation of 8-hydroxyquinoline (131) in acidic anolyte.<sup>196</sup>

Isonicotinic acid (128) has been prepared from 4-picoline (19)<sup>192,193</sup> or from 4-ethylpyridine (132).<sup>194-197</sup> Using 4-ethylpyridine and a Pt anode resulted in higher yields.<sup>193</sup> Platinum was slightly better for oxidizing 4-methylpyridine (19) but 132 was oxidized in good yield at a PbO<sub>2</sub> anode.<sup>192,195</sup> The conclusions reached in each of these separate reports seem to be unclear as to

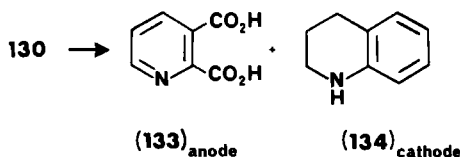


(132)

the best anode material or the best substrate. Perhaps the proper conclusion is that the best electrode material depends on which specific alkylpyridine is being oxidized, but the rationale for such a conclusion is not easy to envision. The lack of specific and detailed information about the processes occurring at the electrode surface would make any conclusion tenuous. The presence of mediators was not helpful in most cases but oxidation of picoline (19) in an alkaline electrolyte did show some promise.<sup>193</sup>

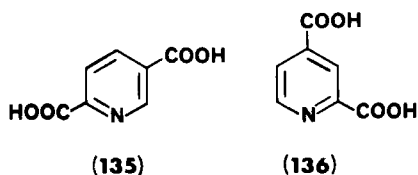
Quinolinic acid (133) was prepared by methods similar to those described for the monocarboxylic acids.<sup>182,183,189-191,196-202</sup> In many cases the resulting diacid was decarboxylated to nicotinic acid (126). Quinoline (130) was simultaneously oxidized to the diacid (133) and reduced to tetrahydroquinoline (134) in one of the rare reports of paired synthesis of pyridine compounds (Scheme 44).<sup>189</sup> An attempt was made to delineate some of the electrode processes for the diacid (133).<sup>200</sup>

Isoscinchomeric (135) and lutidinic (136) acids have also been prepared by similar methods.<sup>203-205</sup> One of the earliest attempts to oxidize alkylpyridines

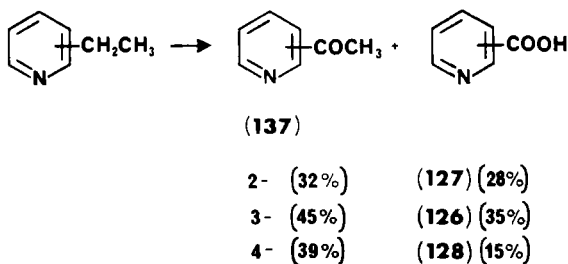


SCHEME 44

anodically was a patented process in which various substituted pyridines were oxidized to the carboxylic acids and subsequently decarboxylated to give "dealkylated" material, pyridine.<sup>207</sup>



A recent patent describes selective oxidations on certain alkylpyridines.<sup>206</sup> For instance, oxidation of the isomeric ethylpyridines gave the isomeric acetylpyridines (**137**) in reasonable yields (Scheme 45). The carboxylic acid was always a co-product. Certain of the dimethylpyridines (**138**, **20**) were oxidized

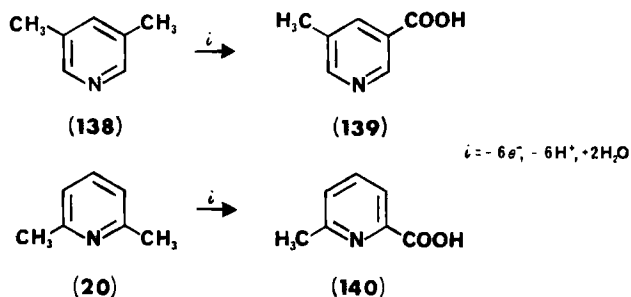


SCHEME 45

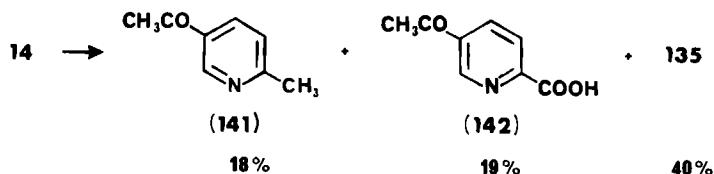
to the methylcarboxylic acid (**139**, **140**) (Scheme 46). Similarly, 2-methyl-5-ethylpyridine (**14**) was selectively oxidized to roughly equal amounts of 2-methyl-5-acetylpyridine (**141**) and 5-acetylpicolinic acid (**142**), although the major product was still the diacid (**135**) (Scheme 47).

Electrochemical fluorination of alkylpyridines proceeds in much the same way as for pyridine itself (Section II,A). The Simmons process gave low yields of perfluoro compounds, the major portion of which resulted from ring fragmentation.<sup>208</sup> Somewhat surprisingly, the yields of perfluoropiperidines

<sup>207</sup> A. Heinemann, British Patent 17,003 (1913).

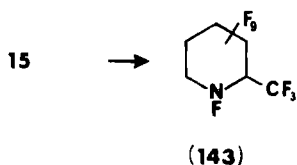


SCHEME 46

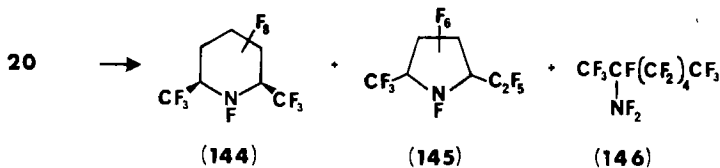


SCHEME 47

increased when the starting pyridine had a 2-alkyl substituent, as does 2-picoline (15), which gave perfluoropiperidine (143) (Scheme 48).<sup>170a</sup> Fluorination of 2,6-lutidine (20) gave a mixture of products of which the major piperidine product was the *cis* isomer (144) (Scheme 49).<sup>208</sup> A ring-contracted product (145) was suspected and an open-chain product (146) was identified.



SCHEME 48



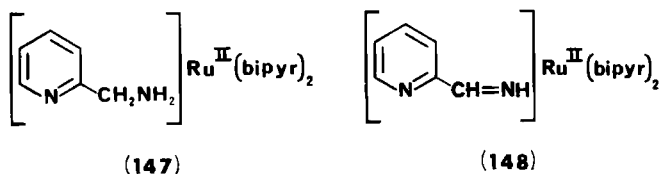
SCHEME 49

<sup>208</sup> R. E. Banks, M. G. Barlow, and M. Nickkho-Amiry, *J. Fluorine Chem.* **14**, 383 (1979).

The mechanistic pathway seems to be quite complex. In order for fluorination to be viable, methods for selective oxidation need to be developed, especially for selective fluorination of the alkyl side chains.

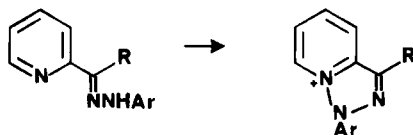
### C. HYDROXYALKYL- AND AMINOALKYLPYRIDINES

The hydroxyalkyl- and aminoalkylpyridines are also almost totally unexplored. The oxidation of various hydroxyalkylpyridines was studied by voltammetry at a platinum anode.<sup>122</sup> The ring substituents had no effect on the position of the discharge wave. Oxidation of the metal-complexed amine **147** to the imine **148** was quantitative.<sup>209</sup>



### D. PYRIDYL ALDEHYDES AND KETONES

Only one report of synthetic value of anodic transformations of pyridyl aldehydes and ketones is known.<sup>210</sup> In this work, a series of hydrazones was converted to the *s*-triazolo[3,4-*a*]pyridinium salts (Scheme 50). The yields were generally high (80–90%).



SCHEME 50

### E. HYDROXY- AND AMINOPYRIDINES

The earliest report of an aminopyridine oxidation is a German patent describing the iodination of 2-aminopyridine to give **149**.<sup>211</sup> The mechanistic implications of voltammetry on several aminopyridines has been

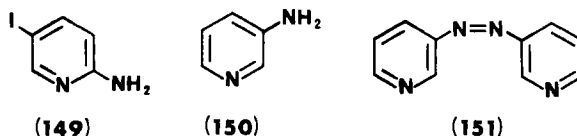
<sup>209</sup> G. M. Brown, T. R. Weaver, F. R. Keene, and T. J. Meyer, *Inorg. Chem.* **15**, 190 (1976); M. J. Ridd and F. R. Keene, *J. Am. Chem. Soc.* **103**, 5733 (1981).

<sup>210</sup> M. Batusić, I. Tabaković, and S. Crljenak, *Croat. Chem. Acta* **54**, 397 (1981).

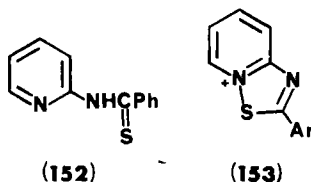
<sup>211</sup> K. Vieweg, German Patent 526,803 [*CA* **25**, 4807 (1931)].



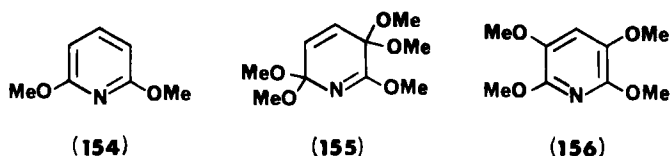
reported.<sup>212,213</sup> Controlled potential electrolysis of 2,3-diamino- and 3-amino pyridine (**150**) gave tars except when **150** was oxidized in an alkaline medium; a low yield of 3,3'-azopyridine (**151**) was observed.



The thiocarboxamide derivative (**152**) of 2-aminopyridine gave a good yield of the thiadiazolopyridinium salt (**153**).<sup>214</sup> Reduction of **153** back to **152** could be done in 90% yield.



The diether **154** was methoxylated to give a mixture of predominantly azaquinone ketal **155** and lesser amounts of tetramethoxypyridine **156**.<sup>215</sup>



## F. PYRIDINIUM SALTS

Oxidation of *N*-alkylpyridinium salts to the 2-pyridones (**157**) is an old, high-yield process that utilizes a mediator, usually potassium ferricyanide (Scheme 51).<sup>216-218</sup> Selectivity for the 2-position was quite high. Iron anodes, an economic and readily machined electrode material, in basic electrolyte are satisfactory. Large variations in current density did not affect the yield. The

<sup>212</sup> I. B. Romanova and L. V. Chervina, *Khim. Geterotsikl. Soedin.* (12), 1654 (1977).

<sup>213</sup> P. G. Desideri, D. Heimler, and L. Lepri, *J. Electroanal. Chem. Interfacial Electrochem.* **88**, 407 (1978).

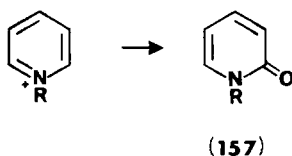
<sup>214</sup> I. Tabaković, M. Trkovnik, M. Batušić, and K. Tabaković, *Synthesis*, 590 (1979).

<sup>215</sup> N. L. Weinberg and E. A. Brown, *J. Org. Chem.* **31**, 4054 (1966).

<sup>216</sup> O. Fischer and K. Neudlinger, *Ber. Dtsch. Chem. Ges.* **46**, 2544 (1913).

<sup>217</sup> K. Neundlinger and M. Chur, *J. Prakt. Chem.* **89**, 466 (1914).

<sup>218</sup> O. Fischer and M. Chur, *J. Prakt. Chem.* **93**, 363 (1916).



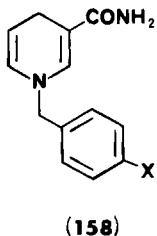
SCHEME 51

technique appears to be general and will work for other heterocyclic quaternary salts such as those of quinoline. However, a technology to produce N-unsubstituted 2-pyridones (157, R = H) would be of commercial interest. Removing the N-alkyl group from 157 can be done, but the technique is expensive and is not always suitable for large-scale processes. Oxidative elimination of a *tert*-butyl group in the 2-position of quaternary salts also having nonoxidizable substituents in the 4- and 6-positions has been observed.<sup>219</sup>

### G. DIHYDROPYRIDINES

Considering the importance of dihydropyridines as intermediates and as valuable products in their own right, the lack of citations directly concerned with anodic oxidation is interesting. Granted, most of the work with  $\text{NAD}^+$  and its analogs have been concerned with both the cathodic reduction and the reverse anodic reaction, but there are hardly any other studies of such systems.

A voltammetric study on various substituted 1,4-dihydropyridines in nonaqueous electrolyte showed that the oxidation is facilitated by electron-donating groups in the 2- or 6-positions and by electron-withdrawing groups in the 3- or 5-positions.<sup>220</sup> The position of the discharge wave of various *p*-benzyl substituted 1,4-dihydropyridines (158) in DMF was related to the Hammett  $\sigma_p$  constants; only in the case of *p*-fluorobenzyl (158, X = F) did the linear correlation break down somewhat.<sup>221</sup>



<sup>219</sup> P. Nesvadba and J. Kuthan, *Collect. Czech. Chem. Commun.* **48**, 511 (1983).

<sup>220</sup> J. Ludvik, J. Klima, J. Volke, A. Kurfuerst, and J. Kuthan, *J. Electroanal. Chem. Interfacial Electrochem.* **138**, 131 (1982).

<sup>221</sup> F. Pavlikova-Raclova and J. Kuthan, *Collect. Czech. Chem. Commun.* **48**, 1408 (1983).

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## $\Delta^2$ -1,2,3-Triazolines

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## I. Introduction

The 1,2,3-triazolines were first discovered by Wolff and collaborators in 1912 during their studies on the action of organic azides on quinones.<sup>1</sup> Triazolines have assumed considerable importance as intermediates in a number of organic syntheses<sup>2-4</sup> and recently as a new class of potential anti-convulsant drugs.<sup>5</sup>

There is no single comprehensive review on the chemistry of 1,2,3-triazolines; earlier reviews cover only selected aspects of triazoline chemistry.<sup>6-13</sup>

This article, which covers the literature up to 1983, endeavors to present a comprehensive, unified survey of the methods of synthesis and reactions of  $\Delta^2$ -1,2,3-triazolines. The chemistry of mono-, bi-, and polycyclic triazolines, as well as that of spiro- and bistriazolines, is considered. The 1,2,3-triazolinones are not included, but a brief account of the chemistry of  $\Delta^3$ - and  $\Delta^4$ -1,2,3-triazolines is given.<sup>14</sup>

## NOMENCLATURE

Three classes of 1,2,3-triazolines can be recognized (Scheme 1). These are identified in *Chemical Abstracts* since 1972 as dihydro derivatives of 1H-1,2,3-triazoles. Early names are shown in parentheses and are still used in many chemical journals and textbooks, the delta or simple numerals indicating the

<sup>1</sup> L. Wolff, *Justus Liebigs Ann. Chem.* **394**, 23, 59, 68 (1912); **399**, 274 (1913).

<sup>2</sup> J. Bourgois, M. Bourgois, and F. Texier, *Bull. Soc. Chim. Fr.*, 485 (1978).

<sup>3</sup> H. C. Van der Plas, "Ring Transformations of Heterocycles," Vol. 1, Academic Press, New York, 1973; H. C. Van der Plas and J. W. Streef, *Aromat. Heteroaromat. Chem.* **5**, 163 (1977) [*CA* **88**, 21419 (1978)].

<sup>4</sup> A. I. Meyers, "Heterocycles in Organic Synthesis." Wiley, New York, 1974.

<sup>5</sup> P. K. Kadaba, *J. Pharm. Sci.* **73**, 850 (1984).

<sup>6</sup> J. H. Boyer and F. C. Canter, *Chem. Rev.* **54**, 42 (1954).

<sup>7</sup> R. Huisgen, R. Grashey, and J. Sauer, in "The Chemistry of Alkenes" (S. Patai, ed.), p. 835. Wiley (Interscience), New York, 1964.

<sup>8</sup> G. L'abbé, *Chem. Rev.* **69**, 345 (1969); *Ind. Chim. Belge* **34**, 519 (1969); **36**, 3 (1971).

<sup>9</sup> T. Sheradsky, in "The Chemistry of the Azido Group" (S. Patai, ed.), p. 331. Wiley (Interscience), New York, 1971.

<sup>10</sup> J. P. Anselme, in "The Chemistry of the Carbon-Nitrogen Double Bond" (S. Patai, ed.), p. 299. Wiley (Interscience), New York, 1970.

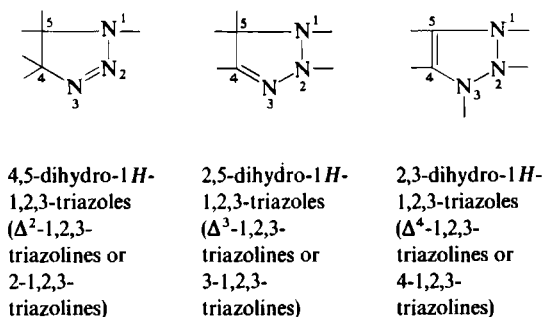
<sup>11</sup> P. K. Kadaba, *Synthesis*, 71 (1973).

<sup>12</sup> P. Scheiner, in "Selective Organic Transformations" (B. S. Thyagarajan, ed.), p. 327. Wiley (Interscience), New York, 1970.

<sup>13</sup> K. T. Finley, *Chem. Heterocycl. Compd.* **39** (1980).

<sup>14</sup> P. K. Kadaba, *Adv. Heterocycl. Chem.* this Volume, pp. 351-361.

position of the double bond in the heterocyclic ring. The triazoline nomenclature is used in this presentation.

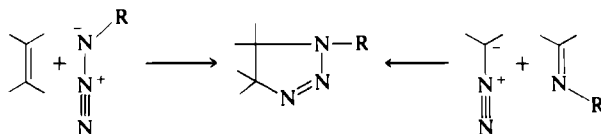


SCHEME 1

Most of the triazoline chemistry is associated with the  $\Delta^2$  compounds, and this is reflected in the abundance of examples of  $\Delta^2$ -1,2,3-triazolines and the rarity of the  $\Delta^3$  and  $\Delta^4$  compounds.

## II. Synthesis of the Triazoline Ring

There are two main approaches to the synthesis of  $\Delta^2$ -1,2,3-triazolines; these involve the union of the C—C and N—N—N fragments as in the olefin—azide additions or alternately building from the C—N and C—N—N moieties as achieved through the imine—diazalkane reactions (Scheme 2). The choice is determined by the type of substitution desired on the triazoline ring. Imines in general can be more easily prepared than the corresponding olefins.

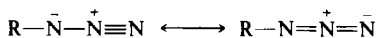


SCHEME 2

Although several early reviews provide brief discussions on olefin—azide additions,<sup>6-9</sup> the greater part of the work on imine—diazalkane reactions is more recent and not covered previously.<sup>10,11</sup> The major methods of triazoline synthesis are outlined in a recent treatise on 1,2,3-triazoles.<sup>13</sup>

## A. FROM AZIDES AND OLEFINS

Organic azides are octet-stabilized 1,3 dipoles of the propargyl-allenyl type, **1a**  $\leftrightarrow$  **1b**.<sup>15</sup> The dipolar character of the azido group<sup>9,15</sup> enables it to



(1a)

(1b)

undergo 1,3-dipolar cycloaddition with olefins forming  $\Delta^2$ -1,2,3-triazolines.<sup>7</sup> The 1,3-dipolar cycloadditions have been extensively reviewed,<sup>15-23</sup> and provide considerable scope for the synthesis of five-membered heterocyclic rings.<sup>20-23</sup> Kinetic studies show that reactions of olefins with organic azides are concerted, stereospecific, cis additions,<sup>24,25</sup> and the olefin geometry is preserved in the triazoline adducts.<sup>26,27</sup> The reactions are characterized by a large negative entropy of activation and a moderate enthalpy of activation, and their rates are essentially independent of solvent polarity.<sup>24,25,28,29</sup> The terminal nitrogen of the azido group binds to the more nucleophilic carbon of the olefin, and this rule is followed by both aryl<sup>7-9,12</sup> and acyl<sup>9,30,31</sup> azides.

Unsymmetrically substituted olefins also exhibit a marked orientational specificity in azide addition reactions<sup>7,9,12,27,32</sup>; the direction of addition is controlled by electronic rather than steric factors.<sup>28</sup> Thus unlike acetylenes,<sup>33</sup>

<sup>15</sup> R. Huisgen, *J. Org. Chem.* **41**, 403 (1976).

<sup>16</sup> R. Huisgen, *Angew. Chem., Int. Ed. Engl.* **2**, 565, 633 (1963); **7**, 321 (1968).

<sup>17</sup> R. Huisgen, *J. Org. Chem.* **33**, 2291 (1968).

<sup>18</sup> R. A. Firestone, *J. Org. Chem.* **33**, 2285 (1968); **34**, 2621 (1969); **37**, 2181 (1972); *J. Chem. Soc., A*, 1570 (1970).

<sup>19</sup> E. Stephan, *Tetrahedron* **31**, 1623 (1975).

<sup>20</sup> G. V. Boyd, *Aromat. Heteroaromat. Chem.* **4**, 106 (1976) [*CA* **86**, 29673h (1977)].

<sup>21</sup> G. V. Boyd, *Aromat. Heteroaromat. Chem.* **5**, 123 (1977) [*CA* **88**, 21418z (1978)].

<sup>22</sup> S. Blechert, *Nachr. Chem., Tech. Lab.* **27**, 173 (1979) [*CA* **91**, 5127k (1979)].

<sup>23</sup> H. Koenig, *Stud. Org. Chem. (Amsterdam)* **6**, 201 (1981) [*CA* **96**, 54212W (1982)].

<sup>24</sup> P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.* **87**, 306 (1965).

<sup>25</sup> R. Huisgen, L. Mobius, G. Mueller, H. Stangl, G. Szeimies, and J. M. Vernon, *Chem. Ber.* **98**, 3992 (1965).

<sup>26</sup> R. Huisgen and G. Szeimies, *Chem. Ber.* **98**, 1153 (1965).

<sup>27</sup> P. Scheiner, *J. Am. Chem. Soc.* **88**, 4759 (1966); **90**, 988 (1968).

<sup>28</sup> R. Huisgen, G. Szeimies, and L. Mobius, *Chem. Ber.* **100**, 2494 (1967).

<sup>29</sup> A. S. Bailey and J. E. White, *J. Chem. Soc. B*, 819 (1966).

<sup>30</sup> R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.* **91**, 933 (1961).

<sup>31</sup> R. Fusco, S. Rossi, and S. Maiorana, *Tetrahedron Lett.*, 1965 (1965).

<sup>32</sup> R. Huisgen, G. Szeimies, and L. Mobius, *Chem. Ber.* **99**, 475 (1966).

<sup>33</sup> T. L. Gilchrist and G. E. Gymer, *Adv. Heterocycl. Chem.* **16**, 33 (1974).



unsymmetrical olefins give only one triazoline isomer, as in the case of phenyl azide-styrene adducts, which are exclusively 1,5-diaryltriazolines.<sup>34</sup> The reaction of *p*-nitrophenyl azide with styrene, however, appears to be an exception (Section II,A,2). The same orientation rules are found valid in additions to enamines,<sup>35-38</sup> enol ethers,<sup>26,39</sup> simple olefins,<sup>40</sup> and olefins bearing electron-withdrawing groups.<sup>7,9,32</sup> As a rule, the electron-releasing groups appear at the 5-position of the triazoline ring and electron-withdrawing substituents at the 4-position, although azide addition to electron-deficient olefinic bonds is not always regiospecific (Section II,A,4 and Section IV,A,3,c). In most instances where two isomers are possible, one isomer usually predominates, often to the exclusion of the other.<sup>41</sup>

Electronic and steric factors dramatically affect the rate of olefin-azide additions. Exceptional reactivity is observed for enamines and enol ethers<sup>7,28</sup>; also a significant effect on the rate of addition from substituents on the phenyl azide.<sup>24,25</sup> Electron-rich azides add particularly easily to electron-poor olefins and vice versa.<sup>7</sup> This is attributed to stabilization of the partial negative or positive charge that develops in the transition state of most cycloadditions<sup>24,28,29,37,42</sup> because the two new  $\sigma$  bonds are not necessarily developed to the same extent.<sup>15-17,19</sup> The sensitivity of azide addition to steric hindrance, first noted by Alder<sup>43-45</sup> and later supported by kinetic results,<sup>29</sup> has been illustrated in the pronounced sluggishness of addition to *cis* isomers compared to the *trans* and in the complete failure of tetramethylethylene to undergo addition even at 60°C.<sup>40</sup>

Molecular orbital models are valuable aids in understanding the reactivity, regioselectivity, and stereospecificity phenomena exhibited by cycloaddition reactions and in predicting reactivity and product identities for addend pairs. Symmetry-energy correlation diagrams indicate that the 1,3-dipolar cyclo-

<sup>34</sup> G. D. Buckley, *J. Chem. Soc.*, 1850 (1954).

<sup>35</sup> R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.* **91**, 849 (1961).

<sup>36</sup> G. Bianchetti, D. Pocar, and P. D. Croce, *Rend.—Ist. Lomb. Accad. Sci. Lett., A* **99**, 316 (1965) [*CA* **65**, 3860g (1966)].

<sup>37</sup> M. E. Munk and Y. K. Kim, *J. Am. Chem. Soc.* **86**, 2213 (1964).

<sup>38</sup> G. Nathansohn, E. Testa, and N. Dimola, *Experientia* **18**, 57 (1962).

<sup>39</sup> R. Huisgen, L. Mobius, and G. Szeimies, *Chem. Ber.* **98**, 1138 (1965).

<sup>40</sup> P. Scheiner, *Tetrahedron* **24**, 349 (1968).

<sup>41</sup> R. Huisgen, H. Gotthardt, and R. Grashey, *Chem. Ber.* **101**, 536 (1968); M. Christl and R. Huisgen, *Tetrahedron Lett.*, 5209 (1968).

<sup>42</sup> M. K. Meilahn, B. Cox, and M. E. Munk, *J. Org. Chem.* **40**, 819 (1975); V. V. Melnikov and J. V. Tselinskii, *Zh. Org. Khim.* **10**, 1360 (1974).

<sup>43</sup> K. Alder and G. Stein, *Justus Liebigs Ann. Chem.* **501**, 1 (1933).

<sup>44</sup> K. Alder and G. Stein, *Justus Liebigs Ann. Chem.* **515**, 165 (1935).

<sup>45</sup> K. Alder, G. Stein, and S. Schneider, *Justus Liebigs Ann. Chem.* **515**, 185 (1935).

addition<sup>15-17,46</sup> reaction is an allowed process by the Woodward–Hoffmann rules.<sup>47-50</sup>

The frontier molecular orbital (FMO) treatment of 1,3-cycloadditions, despite the approximations,<sup>51-56</sup> permits a rational interpretation of the effect of substituents on reactivity<sup>57</sup> and regioselectivity<sup>22,58-60</sup> including exo–endo selectivity in strained cycloalkenes.<sup>61</sup> The reaction rate for an azide passes through a minimum on going from electron-rich to electron-poor olefins, ethylene itself showing the minimum rate<sup>17,28,62</sup>; that for diazomethane increases continuously for the same series of dipolarophiles.<sup>15</sup> The relative reactivity of a 1,3-dipole toward a series of dipolarophiles is determined primarily by the extent of stabilization afforded the transition state by interaction of the frontier orbitals of the two reactants. Reactions fall into three types,<sup>57,63,64</sup> depending on whether the dominant interaction is between the highest occupied molecular orbital (HOMO) of the dipole and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile, or the dipole LUMO and the dipolarophile HOMO, or whether both interactions are of comparable significance. The energies of both HOMOs are increased by

<sup>46</sup> R. Huisgen, *Proc. Chem. Soc., London*, 357 (1961).

<sup>47</sup> R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.* **87**, 395 (1965); *Angew. Chem., Int. Ed. Engl.* **8**, 781 (1969); R. Hoffmann and R. B. Woodward, *Acc. Chem. Res.* **1**, 20 (1968); R. Hoffmann, S. Swaminathan, B. Odell, and R. Gleiter, *J. Am. Chem. Soc.* **92**, 7091 (1970).

<sup>48</sup> A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, R. Grashey, and E. Spindler, *Chem. Ber.* **100**, 2192 (1967).

<sup>49</sup> M. Imoto, *Kagaku (Kyoto)* **31**, 792 (1976) [*CA* **86**, 120139z (1977)]; *Kagaku (Kyoto)* **31**, 878 (1976) [*CA* **86**, 120140t (1977)].

<sup>50</sup> H. Fujimoto and T. Sugiyama, *J. Am. Chem. Soc.* **99**, 15 (1977).

<sup>51</sup> K. N. Houk, *J. Am. Chem. Soc.* **94**, 8953 (1972); K. N. Houk and L. L. Munchausen, *ibid.*, **98**, 937 (1976); K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *ibid.*, **95**, 7287 (1973); K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *ibid.*, 7301; J. Sims and K. N. Houk, *ibid.*, 5798.

<sup>52</sup> W. C. Herndon, *Chem. Rev.* **72**, 157 (1972).

<sup>53</sup> J. Bastide, N. E. Ghandour, and O. Henri Rousseau, *Tetrahedron Lett.*, 4225 (1972).

<sup>54</sup> J. Bastide, N. E. Ghandour, and O. Henri Rousseau, *Bull. Soc. Chim. Fr.*, 2290 (1973).

<sup>55</sup> J. Bastide and O. Henri Rousseau, *Bull. Soc. Chim. Fr.*, 2294 (1973).

<sup>56</sup> R. F. Hudson, *Angew. Chem., Int. Ed. Engl.* **12**, 36 (1973).

<sup>57</sup> R. Sustmann, *Pure Appl. Chem.* **40**, 569 (1974).

<sup>58</sup> K. N. Houk, *Acc. Chem. Res.* **8**, 361 (1975).

<sup>59</sup> J. Bastide, J. P. Maier, and T. Kubota, *J. Electron Spectrosc. Relat. Phenom.* **9**, 307 (1976).

<sup>60</sup> W. Gruendler, *Z. Chem.* **22**, 235 (1982).

<sup>61</sup> R. Gree, F. Tonnard, and R. Carrie, *Bull. Soc. Chim. Fr.*, 1325 (1975); *Tetrahedron* **32**, 675 (1976).

<sup>62</sup> W. Bihlmaier, R. Huisgen, H. V. Reissing, and S. Voss, *Tetrahedron Lett.*, 2621 (1979).

<sup>63</sup> R. Sustmann, *Tetrahedron Lett.*, 2717, 2721 (1971).

<sup>64</sup> R. Sustmann and H. Trill, *Angew. Chem., Int. Ed. Engl.* **11**, 838 (1972).

the presence of electron-donating and conjugating substituents, whereas the energies of both LUMOs are decreased by electron-withdrawing and conjugating substituents.<sup>51</sup> In the case of azide addition to electron-rich olefins, the dominant interaction will be  $\text{HOMO}_{\text{olefin}}-\text{LUMO}_{\text{azide}}$ , whereas  $\text{HOMO}_{\text{azide}}-\text{LUMO}_{\text{olefin}}$  interaction will govern additions to electron-poor olefins. When the HOMO–LUMO energy differences are similar and large, the rate of reaction will be minimal as for ethylene.

The frontier orbital model predicts regioselectivity by determining the relative magnitudes of the coefficients in the HOMO and LUMO of the 1,3-dipole and dipolarophile.<sup>65,66</sup> The favored cycloadduct will be that formed by the privileged union of the atoms with the largest coefficients.<sup>51,54,58</sup> If the energy of interaction is very small for both possible orientations, addition occurs in both directions and two isomeric triazolines will be obtained.<sup>54,67</sup>

An alternative two-step mechanism involving a spin-paired diradical intermediate has also been considered for 1,3-cycloadditions.<sup>18,68,69</sup> However, *ab initio* calculations<sup>70–72</sup> on a wide variety of 1,3-dipoles and dipolarophiles are found to coincide essentially with a synchronous 1,3-cycloaddition mechanism.<sup>15,17</sup> On the other hand, a two-step mechanism passing through two transition states separated by an intermediate has been derived using the MINDO/3 method, and found to be compatible with substituent and solvent effects as well as stereospecificity observed in 1,3-cycloadditions.<sup>73</sup> However, several factors beyond FMO interactions, such as closed shell repulsions, geometrical distortions, polarization, and secondary orbital interactions, all influence mechanisms, rates, and regioselectivities in cycloaddition reactions.<sup>74</sup>

The olefin–azide reaction is a versatile route to the synthesis of 1,4-, 1,5-, and 1,4,5-substituted 1,2,3-triazolines. Although in principle, the reaction can

<sup>65</sup> K. Fukui, *Fortschr. Chem. Forsch.* **15**, 1 (1970).

<sup>66</sup> I. Fleming, "Frontier Molecular Orbitals and Organic Chemical Reactions." Wiley, New York, 1976.

<sup>67</sup> W. Broeckx, N. Overbergh, C. Samyn, G. Smets, and G. L'abbé, *Tetrahedron* **27**, 3527 (1971).

<sup>68</sup> R. A. Firestone, *J. Org. Chem.* **41**, 2212 (1976); *Tetrahedron* **33**, 3009 (1977).

<sup>69</sup> R. D. Harcourt, *Tetrahedron* **34**, 3125 (1978).

<sup>70</sup> D. Poppinger, *J. Am. Chem. Soc.* **97**, 7486 (1975); *Aust. J. Chem.* **29**, 465 (1976).

<sup>71</sup> M. J. S. Dewar, *Discuss Faraday Soc.* **62**, 197 (1977); M. J. S. Dewar, S. Olivella, and H. S. Rzepa, *J. Am. Chem. Soc.* **100**, 5650 (1978).

<sup>72</sup> G. Leroy and M. Sana, *Tetrahedron* **31**, 2091 (1975); **32**, 709, 1379 (1976); G. Leroy, M. T. Nguyen, and M. Sana, *ibid.*, 1529; **34**, 2459 (1978); G. Leroy, *Ann. Soc. Sci. Bruxelles, Ser. I*, **92**, 79 (1978); G. Leroy, M. Sana, L. A. Burke, and M. T. Nguyen, *Quantum Theory Chem. React.* **1**, 91 (1980); P. Blaise and O. Henri Rousseau, *Nouv. J. Chim.* **3**, 369 (1979); M. Sana, G. Leroy, G. Dive, and M. T. Nguyen, *Theochem* **6**, 147 (1982).

<sup>73</sup> J. M. Lluch and J. Bertran, *Tetrahedron* **38**, 1847 (1982).

<sup>74</sup> P. Caramella, K. N. Houk, and L. N. Domelsmith, *J. Am. Chem. Soc.* **99**, 4511 (1977); K. N. Houk, *Top Curr. Chem.* **79**, 1 (1979); *Front. Free Radical Chem. [Pap. Symp.]*, 43 (1980).

be applied to any combination of azide and olefin, it suffers from certain disadvantages as a preparative procedure. Unreactive olefinic bonds require elevated temperatures that may be close to the decomposition temperatures of the azides and/or of the triazoline adducts, which are generally susceptible to thermal decomposition.<sup>12</sup> Cyanogen azide and the lower alkyl azides are unpredictably explosive,<sup>75,76</sup> and thermal decomposition of the azide to the nitrene, as in ethoxycarbonyl azide,<sup>77</sup> may become a competing reaction in some instances.

Based on reactivity, the olefinic double bond may be divided into four classes: (i) angle-strained double bonds and cycloalkenes, (ii) simple, unstrained olefins and conjugated alkenes, (iii) electron-rich double bonds of enamines and enol ethers, and (iv) electron-poor double bonds with electron-withdrawing groups. With regard to the azide component, although aryl and benzyl azides are the most frequently used, satisfactory additions have been described using alkoxycarbonyl azides,<sup>9</sup> bulky trimethylsilyl azides,<sup>78,79</sup> styryl azide,<sup>79</sup> and low-molecular-weight alkyl azides.<sup>80</sup> Addition also occurs with cyanogen azide,<sup>80a</sup> picryl azide,<sup>29</sup> phosphoryl azide,<sup>9</sup> and arylsulfonyl azides,<sup>80b</sup> although the thermal instability of the triazoline adducts has thus far precluded their isolation (Section IV,D,2).

### 1. Angle-Strained Double Bonds and Cycloalkenes

Early work on strained double bonds has been reviewed.<sup>7-9</sup> Double bonds in strained bicyclic systems and medium-sized cycloalkenes are particularly reactive and add azides quantitatively in an exothermic reaction<sup>43-45,81,82</sup> that could be useful in derivatization<sup>83</sup> and quantitative analysis.<sup>84</sup> The reaction of organic azides with strained, olefinic bonds in cyclic systems, first recorded by Alder,<sup>43-45</sup> has been the subject of numerous theoretical and

<sup>75</sup> F. Moulin, *Helv. Chim. Acta* **35**, 167 (1952).

<sup>76</sup> J. H. Boyer, R. Moriarty, B. de B. Darwen, and P. A. S. Smith, *Chem. Eng. News* **42**, 6 (1964).

<sup>77</sup> R. Huisgen and H. Blaschke, *Chem. Ber.* **98**, 2985 (1965).

<sup>78</sup> A. R. Bassindale, A. G. Brook, P. F. Jones, and J. A. G. Stewart, *J. Organomet. Chem.* **152**, C25 (1978).

<sup>79</sup> P. Scheiner, *Tetrahedron* **24**, 2757 (1968).

<sup>80</sup> P. A. S. Smith, J. M. Clegg, and J. Lakritz, *J. Org. Chem.* **23**, 1595 (1958).

<sup>80a</sup> F. D. Marsh and M. E. Hermes, *J. Am. Chem. Soc.* **86**, 4506 (1964).

<sup>80b</sup> A. C. Oehlschlager and L. H. Zalkow, *J. Org. Chem.* **30**, 4205 (1965).

<sup>81</sup> K. Alder and G. Stein, *Justus Liebigs Ann. Chem.* **485**, 211, 223 (1931); K. Alder and E. Windemuth, *Chem. Ber.* **71**, 1939 (1938); K. Alder, H. Krieger, and H. Weiss, *ibid.* **88**, 144 (1955).

<sup>82</sup> D. H. Aue and G. S. Helwig, *Tetrahedron Lett.*, 721 (1974).

<sup>83</sup> W. E. Parham, W. T. Hunter, R. Hanson, and T. Lahr, *J. Am. Chem. Soc.* **74**, 5646 (1952).

<sup>84</sup> A. A. Danish and R. E. Lidov, *Anal. Chem.* **22**, 702 (1950).

experimental studies in recent years and constitutes the major route to the synthesis of a variety of fused-ring triazolines.

The rate of addition of phenyl azide to a series of olefins has been found to parallel the heat of hydrogenation,<sup>25</sup> which is a measure of the degree of strain associated with the molecule.<sup>85</sup> *trans*-Cyclooctene, which contains 9.2 kcal/mol more strain energy than *cis*-cyclooctene, reacts exothermally with phenyl azide, whereas the *cis* isomer requires several months to form the cycloadduct.<sup>29,85-87</sup> In general, as the ring size of *trans* cycloolefins increases, the reactivity decreases because of release of angular strain.<sup>88</sup> The increased reactivity of angle-strained double bonds in cycloadditions is also illustrated by the rapid and quantitative addition of phenyl azide to bicyclo[2.2.1]heptenes such as norbornene<sup>81</sup> and dicyclopentadiene<sup>25,81,89-92</sup>; in the latter, addition occurs exclusively on the more strained double bond of the norbornene nucleus, and the double bond of the cyclopentene nucleus is untouched (Scheme 3).<sup>81,93</sup> At 25°C the phenyl azide reacts with norbornene (Scheme 4) 100 and 5700 times faster than it does with cyclopentene and cyclohexene, respectively.<sup>28</sup>

Azide addition to bicycloheptenes occurs exclusively at the less hindered *exo* side (Schemes 3 and 4) and the triazolines obtained from cyclic olefins with a bridgehead are always the *exo* adducts.<sup>24,25,45</sup> The rule of *exo* addition is supported by the failure of apobornene (**2**) to add aryl azides<sup>43-45</sup>; the methyl group above the double bond severely obstructs the *exo* access<sup>94</sup> and reaction fails. The steric hindrance of *exo* attack fails to induce *endo* addition; although this has been ascribed to steric hindrance by the *endo* hydrogens in the 5- and 6-positions,<sup>95</sup> the latter cannot impair the transition state of *endo* attack any more strongly than the 7-methyl does with regard to *exo* attack.<sup>96</sup> Even in those cases where *endo* adducts are observed,<sup>97-99</sup> the predominating product is always the *exo* adduct.

<sup>85</sup> G. Bianchi and D. Maggi, *J.C.S. Perkin II*, 1030 (1976).

<sup>86</sup> K. R. Henery-Logan and R. A. Clark, *Tetrahedron Lett.*, 801 (1968).

<sup>87</sup> T. Aratani, Y. Nakanisi, and H. Nozaki, *Tetrahedron* **26**, 4339 (1970).

<sup>88</sup> K. Ziegler and H. Wilms, *Justus Liebigs Ann. Chem.* **567**, 1 (1950); K. Ziegler and H. Sauer, *ibid.* **589**, 122 (1954); R. B. Turner and W. R. Meador, *J. Am. Chem. Soc.* **79**, 4133 (1957).

<sup>89</sup> R. E. Banks, M. Bridge, R. Fields, and R. N. Haszeldine, *J. Chem. Soc. C*, 1282 (1971).

<sup>90</sup> R. E. Banks and A. Prakash, *J.C.S. Perkin I*, 1365 (1974).

<sup>91</sup> M. Jurgec, M. Kovačič, B. Stanovnik, M. Tišler, and M. Volk, *J. Heterocycl. Chem.* **12**, 253 (1975).

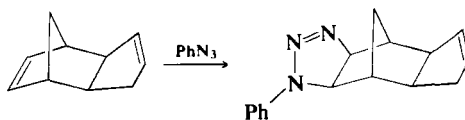
<sup>92</sup> R. S. McDaniel and A. C. Oehlschlager, *Can. J. Chem.* **48**, 345 (1970).

<sup>93</sup> E. Funakubo, I. Moritani, H. Taniguchi, T. Yamamoto, and S. Tichiya, *Chem. Ber.* **96**, 2035 (1963).

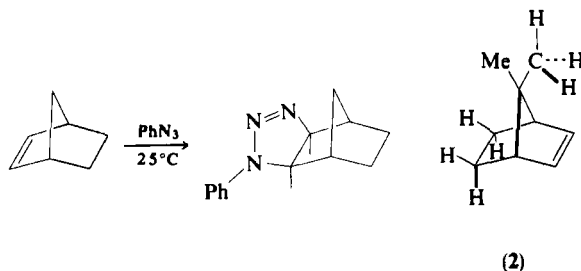
<sup>94</sup> W. Fliege and R. Huisgen, *Liebigs Ann. Chem.*, 2038 (1973).

<sup>95</sup> H. C. Brown, W. J. Hammar, J. H. Kawakami, I. Rothberg, and D. L. Vander Jagt, *J. Am. Chem. Soc.* **89**, 6381 (1967).

<sup>96</sup> R. Huisgen, *Pure Appl. Chem.* **53**, 171 (1981).



SCHEME 3



SCHEME 4

A wide range of organic azides such as alkyl,<sup>80</sup> alkenyl,<sup>79,100</sup> aryl, including dinitrophenyl and picryl,<sup>101-103</sup> heterocyclic,<sup>28,91</sup> trimethylsilyl,<sup>79,104</sup> acyl,<sup>9</sup> phosphoryl,<sup>105</sup> sulfonyl,<sup>106</sup> alkoxy carbonyl,<sup>9</sup> and oxime azides<sup>107</sup> has been found to add to norbornene,<sup>25,79,90,104,105,107-121</sup> its derivatives,<sup>104,106,113,120,122-128</sup> or to related bridged bicyclic

- <sup>97</sup> S. McLean and D. M. Findlay, *Tetrahedron Lett.*, 2219 (1969).
- <sup>98</sup> D. M. Findlay, M. L. Roy, and S. McLean, *Can. J. Chem.* **60**, 3186 (1972).
- <sup>99</sup> B. Halton and A. D. Woolhouse, *Aust. J. Chem.* **26**, 619 (1973).
- <sup>100</sup> A. L. Logothetis, *J. Am. Chem. Soc.* **87**, 749 (1965).
- <sup>101</sup> A. S. Bailey, J. J. Merer, and J. E. White, *Chem. Commun.*, 4 (1965).
- <sup>102</sup> A. S. Bailey and J. E. White, *Chem. Ind. (London)*, 1628 (1965).
- <sup>103</sup> A. S. Bailey and J. J. Wedgwood, *J. Chem. Soc. C*, 682 (1968).
- <sup>104</sup> W. R. Peterson, Jr., B. Arkles, and S. S. Washburne, *J. Organomet. Chem.* **121**, 285 (1976).
- <sup>105</sup> K. D. Berlin and L. A. Wilson, *Chem. Commun.*, 280 (1965).
- <sup>106</sup> R. L. Hale and L. H. Zalkow, *Tetrahedron* **25**, 1393 (1969).
- <sup>107</sup> J. Pleniewicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **25**, 19 (1977) [*CA* **87**, 68248p (1977)].
- <sup>108</sup> J. D. Hobson and J. R. Malpass, *J. Chem. Soc. C*, 1935 (1970).
- <sup>109</sup> R. Huisgen, K. V. Fraunberg, and H. J. Sturn, *Tetrahedron Lett.*, 2589 (1969).
- <sup>110</sup> R. Huisgen, R. Sustmann, and K. Bunge, *Tetrahedron Lett.*, 3603 (1966).
- <sup>111</sup> A. C. Oehlschlager, R. S. McDaniel, A. Thakore, P. Tillman, and L. H. Zalkow, *Can. J. Chem.* **47**, 4367 (1969).
- <sup>112</sup> A. C. Oehlschlager, P. Tillman, and L. H. Zalkow, *Chem. Commun.*, 596 (1965).
- <sup>113</sup> P. Scheiner, *J. Org. Chem.* **30**, 7 (1965).
- <sup>114</sup> D. M. Stout, T. Takaya, and A. I. Meyers, *J. Org. Chem.* **40**, 563 (1975).
- <sup>115</sup> H. Tanida, T. Tsuji, and T. Irie, *J. Org. Chem.* **31**, 3941 (1966).
- <sup>116</sup> K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Lett.*, 869 (1965).

olefins.<sup>25,81,104,107,114,119,121,129-131</sup>  $\alpha$ -Pinene with only moderate strain fails to react with trimethylsilyl azide.<sup>104</sup>

Generally, reaction is carried out in an inert solvent such as benzene,<sup>132</sup> hexane,<sup>24</sup> petroleum ether,<sup>133</sup> carbon tetrachloride, chloroform, or methylene chloride,<sup>128</sup> or often the reactants are mixed directly using excess olefin, which serves as solvent.<sup>25,99,104</sup> The mixture is allowed to stand at room temperature in the dark or is heated at a suitable temperature at which the triazoline is thermally stable. In the absence of solvents, superior yields of adducts are reported.<sup>25,99</sup>

As a rule, the triazoline adducts derived from aromatic azides are relatively more stable and many have been isolated and characterized. Azidoformates<sup>9,111,112,116,129,134</sup> and azidooximes<sup>107</sup> also yield stable adducts; the triazolines **3** and **4** are formed in equal amounts from dicyclopentadiene (Scheme 5),<sup>107</sup> although the orientation of the N=N and C=C bonds has been shown to be as that in **4** for a stable cycloadduct from 6-azidoimidazo[1,2-*b*]pyridazine.<sup>91</sup> The trimethylsilyltriazolines have surprisingly high thermal stability<sup>104</sup>; this is explained by the failure of the trimethylsilyl group to stabilize the negative charge on the nitrogen in the betaine intermediate (Section IV,D,2).<sup>104</sup> For the same reason, triazolines bearing electron-withdrawing groups at the N-1 position are usually too labile to be isolated.

Kinetic studies of the addition of substituted phenyl azide to norbornene show a small substituent effect with a Hammett  $\rho$  value of +0.84, a large

<sup>117</sup> L. H. Zalkow, A. C. Oehlschlager, G. A. Cabat, and R. L. Hale, *Chem. Ind. (London)*, 1556 (1964).

<sup>118</sup> M. Hedayatullah and A. Guy, *J. Heterocycl. Chem.* **16**, 201 (1979).

<sup>119</sup> K. Umamo, H. Taniguchi, H. Inoue, and E. Imoto, *Tetrahedron Lett.*, 247 (1979).

<sup>120</sup> K. B. Becker and M. K. Hohermuth, *Helv. Chim. Acta* **62**, 2025 (1979).

<sup>121</sup> K. Umamo and H. Inoue, *Bull. Univ. Osaka Prefect., Ser. A* **29**, 95 (1980) [*CA* **96**, 68786y (1982)].

<sup>122</sup> M. G. Barlow, G. M. Harrison, R. N. Haszeldine, R. Hubbard, M. J. Kershaw, and D. R. Woodward, *J.C.S. Perkin I*, 2010 (1975).

<sup>123</sup> D. Barractough, J. S. Oakland, and F. Scheinmann, *J.C.S. Perkin I*, 1500 (1972).

<sup>124</sup> B. Halton and A. D. Woolhouse, *Aust. J. Chem.* **26**, 1373 (1973).

<sup>125</sup> J. S. Oakland and F. Scheinmann, *J.C.S. Perkin I*, 800 (1973).

<sup>126</sup> J. D. Roberts, F. D. Johnson, and R. A. Carboni, *J. Am. Chem. Soc.* **76**, 5696 (1954).

<sup>127</sup> P. Scheiner and W. R. Vaughan, *J. Org. Chem.* **26**, 1923 (1961).

<sup>128</sup> P. G. Gassman and J. G. Schaffhausen, *J. Org. Chem.* **43**, 3214 (1978).

<sup>129</sup> T. Sasaki, T. Manabe, and S. Nishida, *J. Org. Chem.* **45**, 479 (1980).

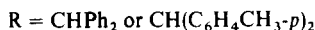
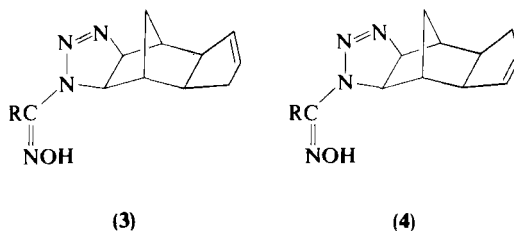
<sup>130</sup> D. C. Horwell and J. A. Deyrup, *Chem. Commun.*, 485 (1972).

<sup>131</sup> N. S. Zefirov, P. P. Kadzyanska, and Y. K. Yur'ev, *J. Gen. Chem. USSR (Eng. Transl.)* **35**, 262 (1965).

<sup>132</sup> H. Taniguchi, T. Ikeda, and E. Imoto, *Bull. Chem. Soc. Jpn.* **51**, 1859 (1978).

<sup>133</sup> P. F. Newton and G. H. Whitham, *J.C.S. Perkin I*, 3077 (1979).

<sup>134</sup> R. J. Stedman, A. C. Swift, and J. R. E. Hoover, *Tetrahedron Lett.*, 2525 (1965).



SCHEME 5

negative entropy of activation of about  $-30$  eu and an enthalpy of activation equal to  $\sim 15$  kcal/mol, indicating a concerted stereospecific addition.<sup>24,25</sup> The positive  $\rho$  value is characteristic of dipolarophiles that are rich in electrons and act as nucleophiles<sup>28,42,135</sup>; thus it may be considered a measure of the privileged interaction between the frontier orbitals.<sup>57,136,137</sup> The sign of the  $\rho$  value has been suggested to indicate in which direction charge transfer is made (as for example, from olefin to azide when  $\rho$  is positive) and its magnitude is a reflection of the HOMO–LUMO energy differences.<sup>57</sup> A linear relation has been observed between the rate constants and the inverse of the energy differences of the frontier orbitals involved in the privileged interaction.<sup>135</sup>

Many explanations have come forth to rationalize the characteristically high reactivity and exo selectivity of the strained double bond in norbornene and related olefins. Originally it was said to arise from a release of ring strain in the transition state,<sup>16,46</sup> analogous to that which occurs in the conversion of norbornene to norbornane.<sup>88</sup> However, both experimental<sup>17</sup> and theoretical<sup>70,72,138</sup> evidence for “early transition states” in cycloadditions indicate that such strain release is inconceivable when the two new  $\sigma$  bonds are still long and weak.<sup>96</sup> Even the decrease in conformational strain resulting from an exo attack<sup>138</sup> is not considered sufficient to defray the high exo–endo ratios of 300<sup>94</sup> and 5000<sup>139</sup> obtained experimentally. Furthermore, rate constants for bicyclohexene (C) and its tricyclic derivative (D) with twice as much strain energy as norbornene,<sup>140</sup> are not larger than that for norbornene,<sup>141</sup> as

<sup>135</sup> J. Bourgois, F. Tonnard, and F. Texier, *Bull. Soc. Chim. Fr.*, 2025 (1976).

<sup>136</sup> J. Bastide, O. Henri Rousseau, and E. Stephan, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, **278**, 195 (1974).

<sup>137</sup> R. Sustmann, *Tetrahedron Lett.*, 963 (1974).

<sup>138</sup> A. Komornicki, J. D. Goddard, and H. F. Schaefer, III, *J. Am. Chem. Soc.* **102**, 1768 (1980).

<sup>139</sup> H. C. Brown, J. H. Kawakami, and K. T. Liu, *J. Am. Chem. Soc.* **92**, 5536 (1970).

<sup>140</sup> N. L. Allinger, *J. Am. Chem. Soc.* **99**, 8127 (1977).

<sup>141</sup> R. Huisgen, P. H. J. Ooms, M. Mingin, and N. L. Allinger, *J. Am. Chem. Soc.* **102**, 3951 (1980).



	 Bicyclo[2.2.1]- heptene (A)	 Bicyclo[2.2.2]- octene (B)	 Bicyclo[2.1.1]- hexene (C)	 Tricyclo[3.3.0.0. <sup>2,6</sup> ] octene (D)	 Cyclohexene (E)	References
Loss of ring strain on hydrogenation (kcal mol <sup>-1</sup> ) (calculated)	4.7	0.51	10.0	8.9	0.15	96
Strain energy (calculated)	23.20	15.15	49.45	52.82	2.76	140
Rate constants for azide addition, $k_2 \times 10^5$ (liter mol <sup>-1</sup> sec <sup>-1</sup> )	112	1.3	—	126	—	141

SCHEME 6

expected if strain release alone were responsible for the high reactivity (Scheme 6).

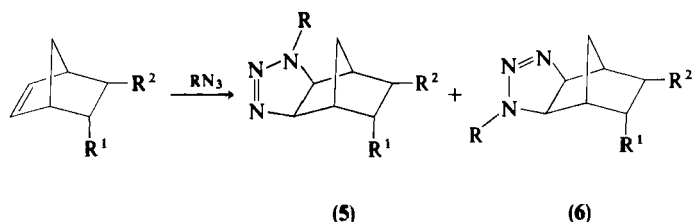
A simple rationalization of exo selectivity is provided by Fukui's concept of "nonequivalent  $\pi$ -orbital extension."<sup>142</sup> Hyperconjugative interactions between the HOMO of the carbon-carbon double bond and the strained methano bridge orbital would lead to larger orbital lobes in the exo position of norbornene than on the endo side (see orbital model A, Scheme 6).<sup>142</sup> Application of the Fukui effect to explain the high reactivity of the strained double bond in norbornene<sup>96</sup> indicates that interaction with the larger exo lobes of norbornene would result in a greater gain of bond energy than the one with the endo lobes.<sup>96</sup> However, the rate constants for azide addition to norbornene and the strained bi- and tricycloalkenes (B, C, and D, Scheme 6) which, owing to symmetry, cannot display nonequivalent  $\pi$ -orbital extension,<sup>141</sup> do not show correlations as expected (Scheme 6).<sup>96</sup> In addition, further MNDO and MINDO/3 calculations for norbornene indicate that the hybridization of the olefinic carbon atoms is normal and there is no  $\pi$ -orbital extension.<sup>143</sup>

It thus appears<sup>96</sup> that the Fukui effect<sup>142</sup> does not operate in the ground state but rather affects the transition state energy. If the hyperconjugative interaction between the  $\pi$  orbital of the double bond and the  $\sigma$ -bond orbitals of the strained methano bridge could be considered to favor the transition state energy in norbornene, then the same structural elements present in C and D would help these olefins also to profit by similar hyperconjugative effects in their respective transition states.<sup>96</sup> This concept is consistent with the early transition states of concerted cycloadditions and the similarity of rate constants for A, C, and D. The bicyclooctene B, on the other hand, with no methano bridge to favor its transition state, exhibits low reactivity in azide addition<sup>127,141</sup> similar to cyclohexene, in spite of its high strain advantage over cyclohexene (Scheme 6).<sup>96</sup>

Whereas azide addition to norbornene occurs stereoselectively to give a single exo isomer, substituted norbornenes give two regioisomeric exo triazoline adducts. When the substituents, regardless of their nature, are not present on the reaction site (Scheme 7)<sup>123,125</sup> their effect on the regioselectivity is not pronounced,<sup>125</sup> although 2-methylnorborn-2-ene (**8**) gives two regioisomers (**8a** and **8b**) with phenyl azide, but 1-methyl-(*E*)-cyclooctene (**7**) does not.<sup>120</sup> Similarly, 1-methylnorbornene has been found to yield with trimethylsilyl azide the syn and anti regioisomers as evidenced by spectroscopic analysis.<sup>104</sup> Further examination of the reaction of phenyl azide with three

<sup>142</sup> S. Inagaki, H. Fujimoto, and K. Fukui, *J. Am. Chem. Soc.* **98**, 4054 (1976).

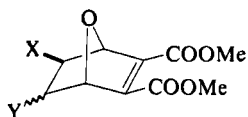
<sup>143</sup> See refs. 36 and 37 to private communication in ref. 96.



R	R <sup>1</sup>	R <sup>2</sup>	%5/6
Ph	NH <sub>2</sub>	Ph	50/50
COOEt	CH <sub>2</sub> CN	H	40/60
COOEt	CH <sub>2</sub> OH	H	40/60

SCHEME 7

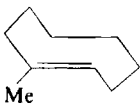
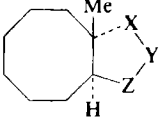
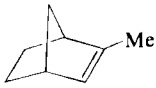
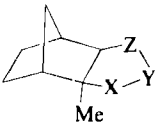

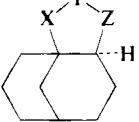

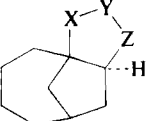

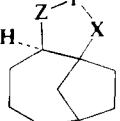
highly strained bicyclononenes (**9–11**), with a view to studying regioselectivity in highly strained systems, also indicates that mixtures of cycloadducts (**9a,b–11a,b**) are formed (Scheme 8).<sup>120</sup> The cycloaddition of phenyl azide to the substituted double bond in 7-oxanorbornene (**6A**) is also presumed to yield two *exo* regioisomers.<sup>143a</sup>



(6A)

Whereas FMO theory correctly predicts the regioselectivity for cycloadditions in simple alkyl-substituted olefinic systems,<sup>51,58</sup> extension of similar calculations for cycloadducts (**7a,b–11a,b**)<sup>120</sup> predicts the formation of regioisomer **a**, although, except in the case of **7** and **8**, the **b** isomer is the predominant one. The differences between prediction and experiment in stereoselectivity have been attributed primarily to double bond rehybridization arising from double bond distortion in bridgehead olefins,<sup>142</sup> which also explains their enhanced reactivity.<sup>96,120</sup> Also double-bond deformation that will alter the normal mixing of alkyl substituent orbitals with localized  $\pi$ -bond orbitals may explain the unexpected formation of **8b**.<sup>120</sup> Attempts to explain the formation of the **b** isomers, based on a two-step diradical mechanism, also have failed.<sup>120</sup>

<sup>143a</sup> N. S. Zefirov, L. P. Prikazchikova, and Yu. K. Yur'ev, *Zh. Obshch. Khim.* **35**, 639 (1965); N. S. Zefirov, A. F. Davydova, and Yu. K. Yur'ev, *ibid.*, 814.

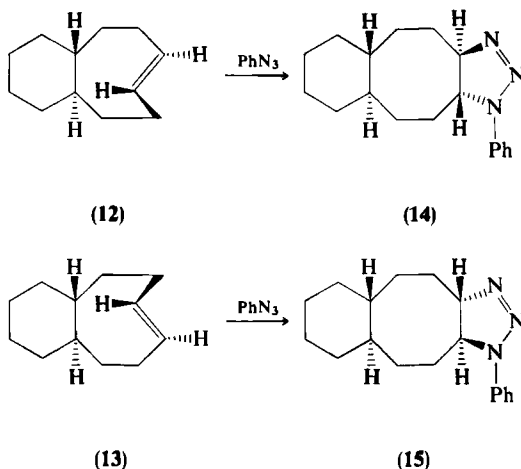
	Olefins	Adducts (a,b)	Ratio	$\frac{a = (-X-Y-Z- = Ph-N=N=N-)}{b = (-X-Y-Z- = -N=N-N-Ph)}$
(7)				7a only
(8)				8a:8b = 75:25
(9)				9a:9b = 33:67
(10)				10a:10b = 45:55
(11)				11a:11b = 33:67

SCHEME 8

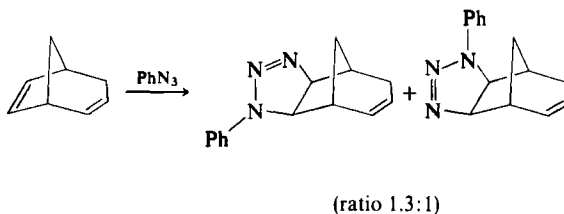
The highly strained bicyclic *trans*-cyclooctenes, both twist (12) and chair (13) forms, are exceptions and are reported to react with phenyl azide to yield a single regioselective addition product (14 and 15, respectively) (Scheme 9).<sup>133</sup>

Regioisomerism in azide additions is also evident in unsymmetrical dienes with two unequally strained double bonds.<sup>89,92,144</sup> Reaction occurs preferentially at the angle-strained double bond,<sup>25,81,89-92</sup> and two isomeric *exo*-monotriazoline adducts are obtained.<sup>81,93</sup> The ratios of the triazoline isomers from the reaction of phenyl azide and bicycloocta-2,6-diene, as deduced from their NMR spectra, indicate that the major isomer is the one that results from the terminal azido nitrogen attacking the olefinic carbon more removed from the unreactive double bond (Scheme 10).<sup>92</sup> Similar reactions

<sup>144</sup> R. S. McDaniel, *Diss. Abstr. Int. B* 33, 119 (1972).



SCHEME 9

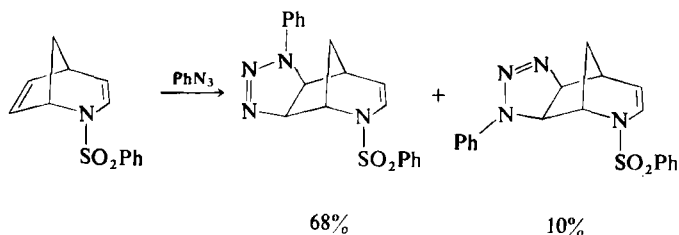


SCHEME 10

also occur with *endo*-dicyclopentadiene and 5-methylene-2-norbornene.<sup>92</sup> Polyfluorodicyclopentadienes react smoothly and quantitatively with phenyl azide at room temperature when no fluoro substituent is present on the strained double bond<sup>145</sup>; the  $\text{FC}=\text{CF}$  bond requires higher reaction temperature, and the isolated product is the aziridine derivative presumably arising from the two isomeric triazoline intermediates.<sup>89</sup>

Likewise, two *exo* regioisomers are obtained from the addition of phenyl azide to 2-azabicycloocta-3,6-diene<sup>132</sup>; no *endo* or bisadducts have been detected. The isomeric triazolines can be distinguished by their NMR chemical shifts, the coupling constants, the spin-spin decouplings, and the nuclear Overhauser effects (Section III). The *N*-phenylsulfonyl group in the major product is on the opposite side of the molecule from the phenyl group (Scheme 11). The exostereoselectivity and double-bond reactivity at the C-6/C-7

<sup>145</sup> W. Carpenter, A. Haymaker, and D. W. Moore, *J. Org. Chem.* **31**, 789 (1966).



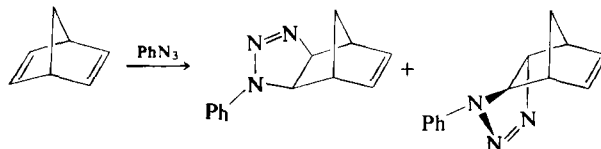
SCHEME 11

location are a consequence of the nonequivalent  $\pi$ -orbital extension,<sup>142</sup> which exceeds that of the enamine double bond.<sup>132</sup>

The regiochemistry of trimethylsilyl azide addition to dicyclopentadiene is not clearly indicated in the proton NMR spectrum; <sup>13</sup>C-NMR studies may provide a definite answer.<sup>104</sup> The same is true of the triazoline adducts from phenyl azide and 7-oxa- and 7-azabenzonorbomadiene, respectively.<sup>145a</sup>

The addition of aryl azides to cyclic dienes in which both double bonds are strained, leads to the formation of mono- or bistriazoline adducts.<sup>25,97,98,104,115,146-148</sup> A monoadduct is not obtained from the reaction of trimethylsilyl azide and norbornadiene, inasmuch as it is less stable than the bisadduct and undergoes a retro Diels-Alder reaction (Section IV,A,5).<sup>104</sup> The formation of two exo isomers of the bisadduct, with the trimethylsilyl groups in the syn and anti positions, is indicated by the NMR spectrum,<sup>104</sup> although the isolated product is the anti isomer.

Exo addition is not always the rule with cyclic dienes, and endo adducts have been identified in several instances. Although in earlier work phenyl azide was thought to yield with excess norbornadiene only a single exo adduct,<sup>25</sup> later work indicates that the endo isomer is also formed in an exo-endo ratio of 11/1 (Scheme 12).<sup>97</sup> In excess azide, four isomeric bistriazolines have been



SCHEME 12

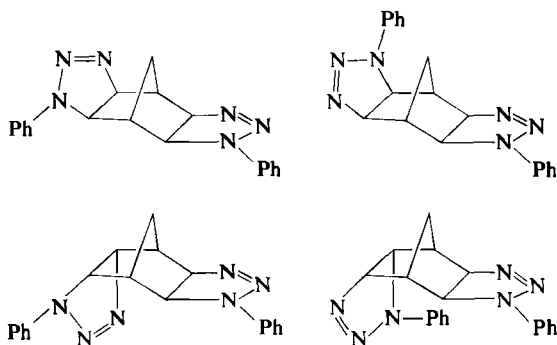
<sup>145a</sup> G. Wittig and L. Pohmer, *Angew. Chem.* **67**, 348 (1955); *Chem. Ber.* **89**, 1334 (1956); G. Wittig and B. Reichel, *ibid.* **96**, 2851 (1963).

<sup>146</sup> M. G. Barlow, R. N. Haszeldine, and W. D. Morton, *Chem. Commun.*, 931 (1969).

<sup>147</sup> B. Halton and A. D. Woolhouse, *Tetrahedron Lett.*, 4877 (1971).

<sup>148</sup> L. A. Paquette, R. J. Haluska, M. Short, and L. K. Read, *J. Am. Chem. Soc.* **94**, 529 (1972).

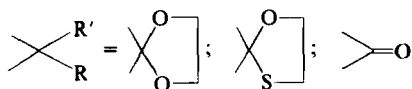
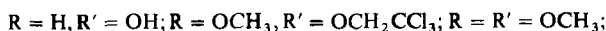
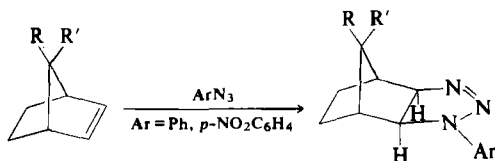
detected, although the major product is the *exo* bisadduct; there is no evidence for the formation of the *endo-endo* isomer (Scheme 13).<sup>97,98</sup> On the other hand,



SCHEME 13

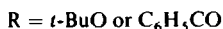
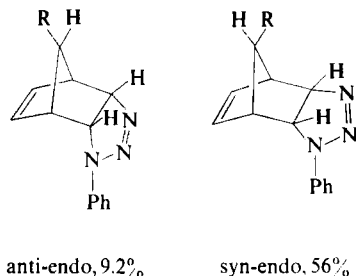
the *exo*-monotriazoline adduct is found to be the sole product of the reaction of dimethylnorbornadiene-2,3-dicarboxylate and phenyl azide, with addition occurring only at the unsubstituted double bond.<sup>99</sup> A similar monoaddition occurs with benzenesulfonyl azide, but only the aziridines are isolated.<sup>119,121</sup>

The reaction of aryl azides with a number of 7-substituted norbornenes and norbornadienes has been investigated (Scheme 14).<sup>128</sup> Although bulky substituents in the 7-position slow down addition,<sup>43-45</sup> good yields of adducts have been obtained in most cases by carrying out the reaction for several days. NMR analysis indicates exclusive *exo* stereochemistry for the products, and when the 7-hydroxyl is in the *anti* position, the direction of azide addition is reversed (Scheme 14).<sup>99</sup>



SCHEME 14

The cycloaddition of phenyl azide with 7-*t*-butoxynorbornadiene proceeds anomalously to produce predominantly the *syn*- and *anti-endo*-triazolines (Scheme 15),<sup>99,149</sup> isolated by preparative thin layer chromatography and



SCHEME 15

identified by NMR spectroscopy.<sup>99</sup> Only 1.4% of the product consists of the *syn*- and *anti-exo* adducts. A similar *endo* selectivity is also observed in the 7-benzoyl compound, although only 4% of the pure *syn*- and *anti-endo* adducts has been isolated.<sup>99</sup>

On the other hand, 7-azabenzonorbornadiene bearing a *tert*-butoxycarbonyl substituent in the 7-position, in spite of the bulky 7-substituent, exhibits *exo* selectivity in the addition of ethoxycarbonyl azide.<sup>129</sup> Benzenesulfonyl and tosyl azides, however, give rise to a complex mixture from which no products could be characterized.<sup>129</sup> The phenyl azide adduct has been obtained in 88% yield, but the stereochemistry is not known.<sup>149a</sup> An orbital model for the effect of the 7-substituent, as a through-space interaction between the substituent and the *syn* double bond, has been suggested,<sup>150</sup> and generalizations that may help to predict the *syn*-*anti* selectivity in these compounds have been developed.<sup>99,149,150</sup>

Isodrin, used for the synthesis of "cagelike" compounds, forms an *exo* adduct with *t*-butyl azidoformate (Scheme 16).<sup>134</sup>

Triazoline adducts from phenyl azide and *syn*-sesquinorbornene (**16**)<sup>152</sup> and its *exo* anhydride derivative (**17**)<sup>153</sup> have been prepared and characterized

<sup>149</sup> G. W. Klumpp, A. H. Veefkino, W. L. de Graaf, and F. Bickelhaupt, *Justus Liebigs Ann. Chem.* **706**, 47 (1967).

<sup>149a</sup> L. A. Carpino and D. E. Barr, *J. Org. Chem.* **31**, 764 (1966).

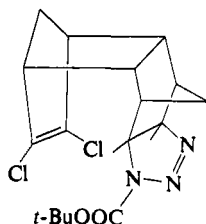
<sup>150</sup> P. V. Alston and R. M. Ottenbrite, *J. Heterocycl. Chem.* **14**, 1443 (1977).

<sup>151</sup> W. H. Watson, J. Galloy, P. D. Bartlett, and A. A. M. Roof, *J. Am. Chem. Soc.* **103**, 2022 (1981).

<sup>152</sup> L. A. Paquette, R. V. C. Carr, M. C. Bohm, and R. Gleiter, *J. Am. Chem. Soc.* **102**, 1186, 7218 (1980).

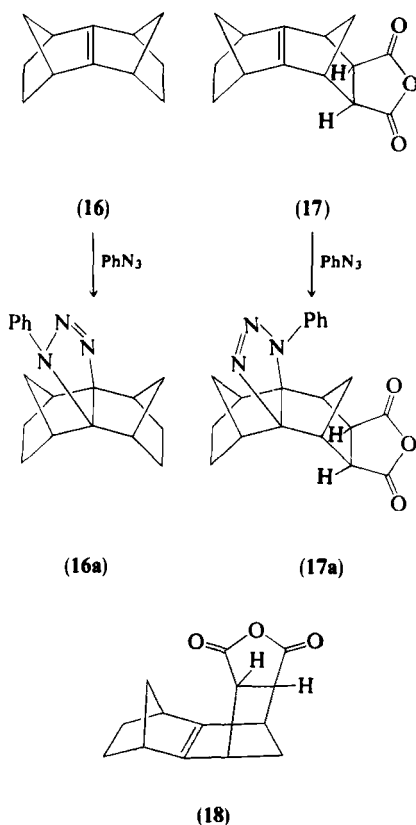
<sup>153</sup> L. A. Paquette, K. Ohkata, and R. V. C. Carr, *J. Am. Chem. Soc.* **102**, 3303 (1980).





SCHEME 16

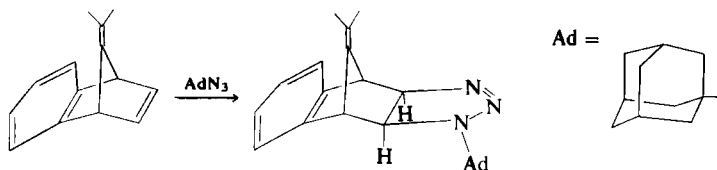
by X-ray diffraction;<sup>151</sup> the anti-endo anhydride (**18**) does not react (Scheme 17).<sup>151</sup> The double bond system of **18** as shown by X-ray studies is planar, whereas that of syn compounds **16** and **17** has a dihedral angle of 162–164° between the planes of the two rings sharing the double bond, spreading the



SCHEME 17

methylene bridges apart.<sup>151</sup> This deviation from planarity leads to double bond deformation in the syn compounds with an increase in  $\pi$ -electron density above the plane, and phenyl azide addition occurs exclusively from the C-9/C-10 side.<sup>151</sup> X-Ray studies of **16** indicate strong steric interactions between backside hydrogens, and yet its reactivity could be due to initiation of double bond rehybridization in the ground state hydrocarbon itself.<sup>151</sup>

The rare bridgehead azide 1-azidoadamantane<sup>154</sup> reacts with a number of strained olefins (see, e.g., Scheme 18) to give good yields of cycloadducts with



SCHEME 18

the exo configuration.<sup>155</sup> A comparison of the FMO of phenyl azide and 1-azidoadamantane<sup>155</sup> indicates the latter to have relatively higher LUMO energy and hence lesser reactivity than phenyl azide toward olefinic bonds, and, indeed, reaction proceeds smoothly only upon heating in toluene. Although the steric bulkiness of the adamantyl group has a considerable effect on reactivity, its striking thermal stability allows for longer heating periods.<sup>155</sup>

Progress in the areas of phot scrambling and valence bond isomerization reactions in aromatic<sup>156</sup> and heteroaromatic compounds<sup>157</sup> has led to the study of new cyclic systems with strained olefinic double bonds.<sup>158</sup> Dewar benzene, Dewar thiophene, benzvalene, and their heteroaromatic counterparts substituted with fluoro and/or perfluoroalkyl substituents have been synthesized and their reactions with phenyl azide have been investigated.

The strained double bonds in Dewar benzene and thiophene make them good dipolarophiles in 1,3-cycloadditions. The hexamethyl,<sup>148</sup> 1,3,5-trimethyl, and perfluoro-1,3-dimethyl<sup>122</sup> Dewar benzenes all yield a monoadduct by reaction with phenyl azide. The hexafluoro derivative, however, gives, depending on the conditions, either a monoadduct (**19**) or a mixture of mono- and bisadducts accompanied by an aziridine resulting from thermolysis of the triazoline ring system (Scheme 19).<sup>146</sup>

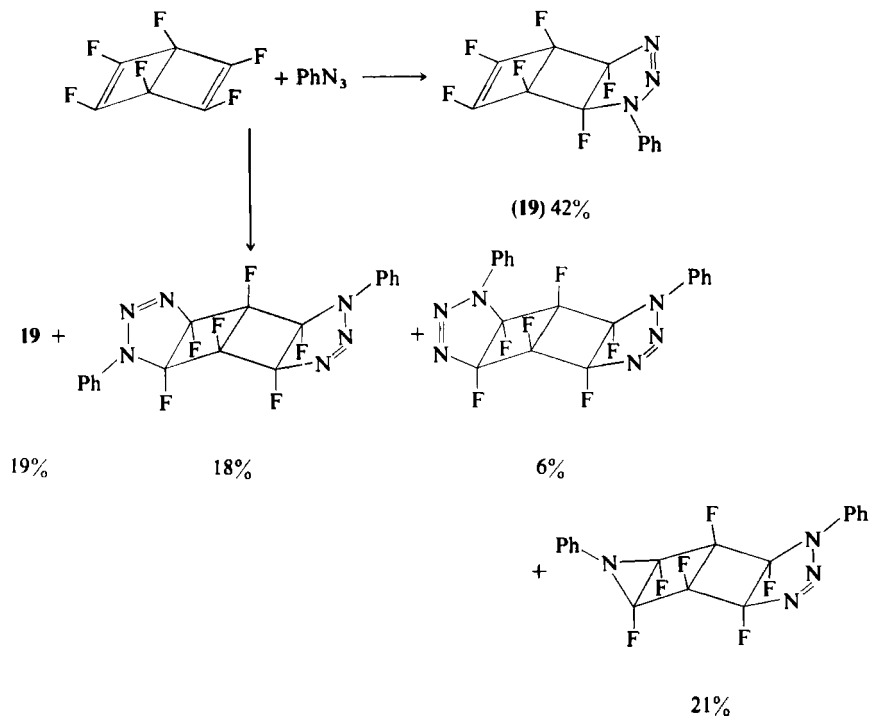
<sup>154</sup> T. Sasaki, S. Eguchi, T. Katada, and O. Hiroaki, *J. Org. Chem.* **42**, 3741 (1977).

<sup>155</sup> T. Sasaki, S. Eguchi, M. Yamaguchi, and T. Esaki, *J. Org. Chem.* **46**, 1800 (1981).

<sup>156</sup> E. E. van Tamelen and S. P. Pappas, *J. Am. Chem. Soc.* **84**, 3789 (1962).

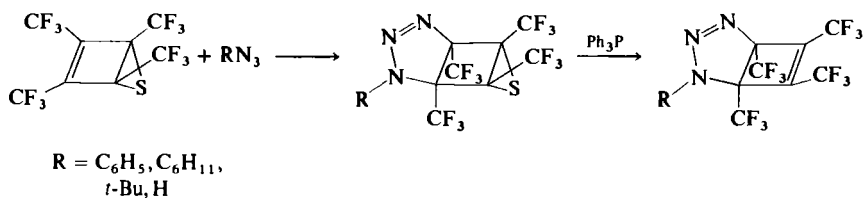
<sup>157</sup> R. D. Chambers, W. K. R. Musgrave, and K. C. Srivastava, *Chem. Commun.*, 264 (1971).

<sup>158</sup> M. G. Barlow, R. N. Haszeldine, and J. G. Dingwall, *J.C.S. Perkin I*, 1542 (1973); Y. Kobayashi and A. Ohsawa, *Tetrahedron Lett.*, 2643 (1973).



SCHEME 19

The perfluoroalkyl Dewar thiophene, unlike Dewar benzene, reacts with aryl, alkyl, as well as the unusual hydrogen azide at room temperature to give 80–94% yields of cycloadducts; the *t*-butyl compound (Scheme 20)<sup>159–161</sup> is



SCHEME 20

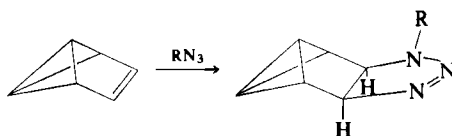
<sup>159</sup> Y. Kobayashi, I. Kumadaki, A. Ohsawa, and A. Ando, *J. Am. Chem. Soc.* **99**, 7350 (1977).

<sup>160</sup> Y. Kobayashi, I. Kumadaki, A. Ohsawa, Y. Sekine, and A. Ando, *Heterocycles* **6**, 1587 (1977).

<sup>161</sup> Y. Kobayashi, A. Ando, K. Kawada, A. Ohsawa, and I. Kumadaki, *J. Org. Chem.* **45**, 2962 (1980).

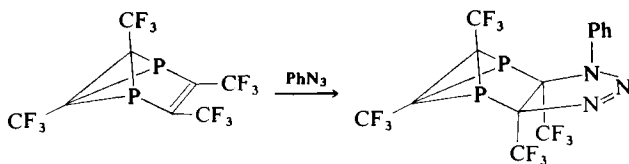
an exception. These novel triazoline ring systems are quite stable, perhaps because of the electronic effect of the trifluoromethyl groups.<sup>161</sup> They can be desulfurized with triphenylphosphine to give unstable cyclobutatriazolines (Scheme 20).<sup>161</sup>

Benzvalene is a highly strained tricyclohexene that reacts with aryl and acyl azides to give isolable triazolines including the one from *p*-toluenesulfonyl azide (Scheme 21)<sup>162</sup>; the latter usually is quite labile and yields only the



SCHEME 21

aziridine.<sup>166</sup> Hydrogen azide, however, unlike in the case of Dewar thiophene (Scheme 20),<sup>159-161</sup> yields only the aziridine, a new valence isomer of azepine.<sup>162</sup> The simplicity of these reactions opens up a route to a wide range of quadricyclic triazoline compounds. 1,3-Cycloaddition reactions of trifluoromethyl-substituted benzvalenes have been reviewed.<sup>163</sup> Trifluoromethylated diphospha-benzvalene, the first example of a heterocyclic benzvalene,<sup>164,165</sup> compares with the benzene analog hexakis(trifluoromethyl)benzvalene in its reactivity in spite of the steric hindrance posed by the trifluoromethyl groups (Scheme 22).<sup>165</sup>



SCHEME 22

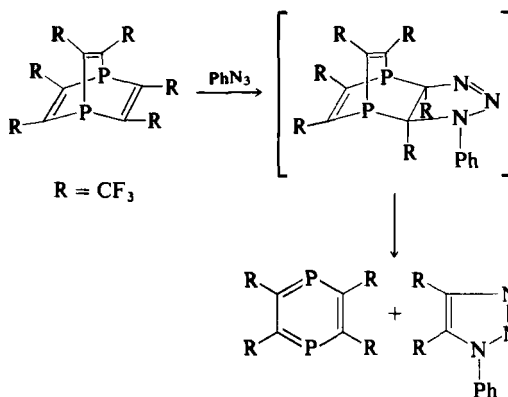
<sup>162</sup> M. Christl, *Angew. Chem., Int. Ed. Engl.* **12**, 660 (1973); M. Christl and H. Leininger, *Tetrahedron Lett.*, 1553 (1979).

<sup>163</sup> Y. Kobayashi, I. Kumadaki, and Y. Hanzawa, *Yuki Gosei Kagaku Kyokaiishi* **37**, 183 (1979) [*CA* **91**, 19198w (1979)].

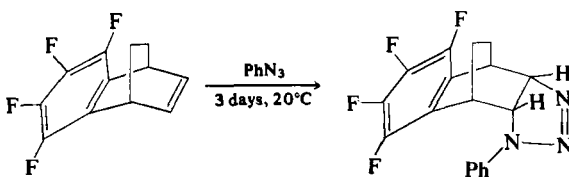
<sup>164</sup> R. D. Chambers, J. A. H. MacBride, J. R. Maslakiewicz, and K. C. Srivastava, *J.C.S. Perkin I*, 396 (1975).

<sup>165</sup> Y. Kobayashi, S. Fujino, H. Hamana, Y. Hanzawa, S. Morita, and I. Kumadaki, *J. Org. Chem.* **45**, 4683 (1980).

Tetrafluorobenzobarrelene, a bicyclooctatriene, gives a triazoline adduct that even under mild conditions undergoes a cycloreversion reaction with unusual ease (Section IV,A,5).<sup>166</sup> A similar cycloreversion occurs in the phenyl azide adduct from hexakis(trifluoromethyl)-1,4-diphosphabarrelene (Scheme 23).<sup>167,168</sup> The dihydrobarrelene compound forms a stable endo adduct (Scheme 24); thus the instability of the barrelene-phenyl azide adducts may be from disruption of the stabilization of the barrelene ring by the six  $\pi$



SCHEME 23



SCHEME 24

electrons.<sup>169</sup> However, the dihydrobarrelene adduct from ethyl azidoformate undergoes a facile cycloreversion.<sup>169</sup> Endo addition in the barrelenes demonstrates the greater steric accessibility of the double bond from the endo side.<sup>169</sup>

Homoadamantene reacts with phenyl and tosyl azides, although the fused triazoline system is isolable only in the phenyl azide reaction (Scheme 25).<sup>170</sup>

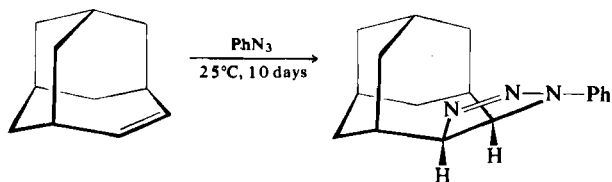
<sup>166</sup> I. N. Vorozhtsov and V. A. Barkhash, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 144 (1969).

<sup>167</sup> Y. Kobayashi, H. Hamana, S. Fujino, A. Ohsawa, and I. Kumadaki, *J. Org. Chem.* **44**, 4930 (1979).

<sup>168</sup> Y. Kobayashi, I. Kumadaki, A. Ohsawa, and H. Hamana, *Tetrahedron Lett.*, 867 (1977).

<sup>169</sup> N. N. Povolotskaya, M. I. Kollegova, E. I. Berus, and V. A. Barkhash, *Zh. Org. Khim.* **6**, 2331 (1970).

<sup>170</sup> T. Sasaki, S. Eguchi, and S. Hattori, *Heterocycles* **11**, 235 (1978).



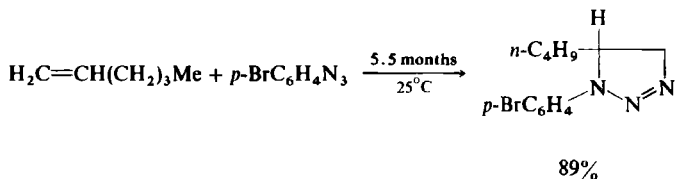
SCHEME 25

Cycloaddition reactions of phenyl and tosyl azides to the strained double bond in cyclopropenes have been investigated.<sup>170a</sup> The reaction products from 3,3-dimethylcyclopropene indicate that the initially formed intermediate is a normal 1,3-dipolar adduct. Tetrachlorocyclopropene yields the primary adducts with several aryl azides.<sup>170b</sup> However, cyclopropenedicarboxyl ester gives only unstable triazolines with phenyl and methyl azides.<sup>170c</sup>

## 2. Unstrained and Inactivated Double Bonds

a. *Double Bonds of Linear and Unstrained Cyclic Olefins.* Unstrained olefinic double bonds not activated by electron-withdrawing or -releasing groups react slowly with azides and require higher reaction temperatures or prolonged reaction periods at lower temperatures.<sup>40,86,144</sup> Unsubstituted olefins occupy the lowest position on the U-shaped reactivity curve toward azides, flanked on either side by the electron-rich and electron-poor olefins.<sup>17,28,62</sup> This changing reactivity is as expected from molecular orbital models (Section II,A).<sup>57,63,64</sup>

By carefully controlling the temperature and duration of reaction so as to avoid triazoline thermolysis, satisfactory yields can be achieved. A generally satisfactory procedure is to treat the azide with excess olefin at 40–70°C and terminate the reaction after 20% nitrogen evolution from the triazoline decomposition is observed.<sup>40</sup> Increased yields are obtained at lower temperatures, although prohibitively long reaction times are required (Scheme 26).<sup>40</sup>



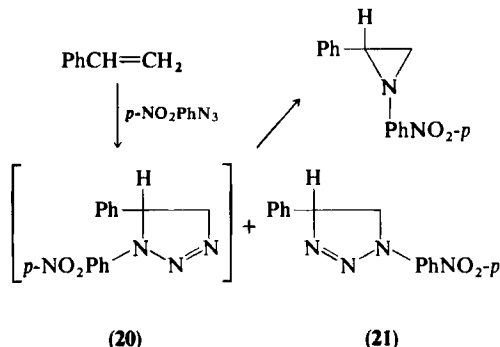
SCHEME 26

<sup>170a</sup> D. H. Aue, R. B. Lorens, and G. S. Helwig, *J. Org. Chem.* **44**, 1202 (1979).

<sup>170b</sup> E. V. Dehmlow and U. D. Naser, *J. Chem. Res., Synop.*, **40** (1978) [*CA* **89**, 24235u (1978)].

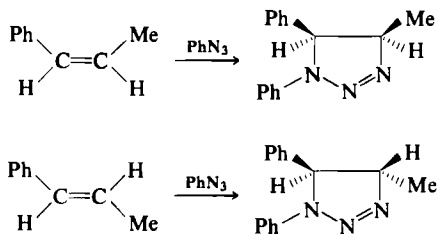
<sup>170c</sup> F. N. Michel and C. Buchecker, *Tetrahedron Lett.* **31**, 2659 (1969).

Orientation of addition is in accordance with general mechanistic considerations for 1,3-dipolar cycloadditions, and is highly regioselective.<sup>27,34,40,171-174</sup> The addition of *p*-nitrophenyl azide to styrene, however, is an exception; the triazoline (21) and an aziridine obtained from thermolysis of the isomeric triazoline (20) are the products (Scheme 27).<sup>110,175</sup>



SCHEME 27

Phenyl azide undergoes stereospecific addition to (*Z*)- and (*E*)-methylstyrene as shown in Scheme 28.<sup>27,144</sup> Although the reaction is sensitive to steric effects, as evidenced by the failure of phenyl azide to add to tetramethylethylene,<sup>40</sup> the orientation is controlled by electronic rather than steric factors.<sup>27,34,40</sup>



SCHEME 28

The potential energy surface for the cycloaddition of hydrazoic acid to ethylene by the MINDO/2 method indicates a four-center, one-step process with the calculated enthalpy of formation of the transition state complex

<sup>171</sup> D. H. Aue, R. B. Lorens, and G. S. Helwig, *Tetrahedron Lett.*, 4795 (1973).

<sup>172</sup> J. K. Crandall and W. W. Conover, *J. Org. Chem.* **39**, 63 (1974).

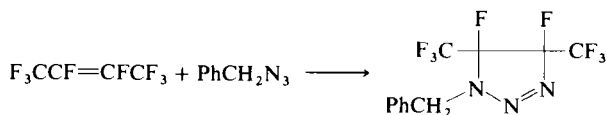
<sup>173</sup> J. K. Crandall, W. W. Conover, and J. B. Komin, *J. Org. Chem.* **40**, 2042 (1975).

<sup>174</sup> O. Gerlach, P. L. Reiter, and F. Effenberger, *Liebigs Ann. Chem.*, 1895 (1974).

<sup>175</sup> R. Huisgen, R. Sustmann, and K. Bunge, *Chem. Ber.* **105**, 1324 (1972).

(14.6 kcal/mol) comparing well with the experimental value (18–20 kcal/mol).<sup>176</sup> A four-centered, synchronous mechanism is also proposed for the reaction of  $\beta$ -ethoxyethyl azide with 1-alkenes ranging from octene through tridecene, based on cycloaddition kinetics including thermodynamic parameters.<sup>177</sup>

Perfluoro olefins combine with azides more slowly than their hydrocarbon counterparts.<sup>145</sup> Thus benzyl azide adds slowly to perfluoropropene and -butene to give the corresponding triazolines (Scheme 29), which exhibit unusual thermal stability.<sup>145</sup>



SCHEME 29

Alkenylsilanes react with silyl azide and other organic azides to give bisallylenamines and silylaziridines, respectively, via unstable triazoline intermediates.<sup>78</sup> Heating trimethylsilyl azide with cyclohexene or vinyltriethylsilane for 10 days affords a modest yield of the respective aziridine,<sup>178</sup> but with carefully purified trimethylsilyl azide, even after 2 weeks of reflux, no olefin consumption is indicated.<sup>104</sup> Unstable triazoline intermediates are also formed from the reaction of cyanogen azide,<sup>80a</sup> picryl azide,<sup>29</sup> and arylsulfonyl azides<sup>80b</sup> with unactivated olefinic bonds.

Because groups capable of stabilizing the positive charge on the olefinic carbon in the transition state should facilitate reaction (i.e., increase the olefin HOMO energy), conjugated olefins could be anticipated to be reasonably reactive in azide additions. Thus styrene reacts twice as fast as 1-heptene,<sup>7,28</sup> whereas cyclohexene, even after 3 months, gives no detectable addition<sup>40,43,44</sup>; 1,3-cyclohexadiene and *p*-bromophenyl azide form an adduct in 3 days (Scheme 30).<sup>40</sup> Butadienes react similarly and afford a method for preparing vinyltriazolines,<sup>40</sup> whereas cyclopropylethylenes yield 5-cyclopropyl-substituted triazolines.<sup>174</sup> Cycloheptene,<sup>79</sup> 2,5-dihydrofuran (**22**),<sup>79</sup> and 3-pyrroline (**23**)<sup>79,179</sup> also give satisfactory addition with aryl azides.

Triazolines are also obtained by addition of aryl azides to indene,<sup>34,180</sup> methoxycarbonylindene,<sup>181</sup> and 1,2-dihydronaphthalene.<sup>181</sup> Azide addition

<sup>176</sup> S. A. Zacheslavskii, V. V. Mel'nikov, and B. V. Gidasov, *Zh. Org. Khim.* **15**, 677 (1979).

<sup>177</sup> G. A. Lanovaya, V. F. Mishchenko, and T. A. Kuz'micheva, *Zh. Org. Khim.* **12**, 2496 (1976).

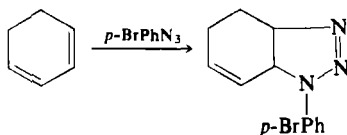
<sup>178</sup> E. Ettenhuber and K. Ruhlmann, *Chem. Ber.* **101**, 743 (1968).

<sup>179</sup> D. Pocar, L. M. Rossi, and P. Trimarco, *J. Heterocycl. Chem.* **17**, 267 (1980).

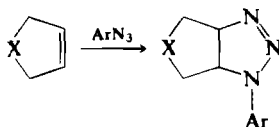
<sup>180</sup> J. Jaz, E. Draquez de Hault, and R. Navette, *Tetrahedron Lett.*, 2751 (1965).

<sup>181</sup> J. Vebrel, E. Cerutti, and R. Carrie, *C. R. Hebd. Seances Acad. Sci., Ser. C* **288**, 351 (1979) [*CA* **91**, 91391w (1979)].





SCHEME 30



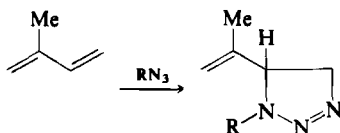
(22) X = O

(23) X = NH

to styrene in ethanol gives twice as much triazoline as in ethyl acetate<sup>182</sup> because of enhanced charge stabilization in the transition state.

The reactivity of cyclopentene in phenyl azide addition exceeds that of cyclohexene by a factor of 56.<sup>28</sup> The envelope structure of cyclopentene, with C-4 serving as the flap, is similar to the bridgehead in norbornene and thus benefits from the Fukui effect in its transition state, much in the same manner as norbornene, though to a smaller degree.<sup>96</sup>

Several heteroaromatic azides react with isoprene; addition occurs as expected at the less hindered double bond, and satisfactory yields of triazolines are obtained after several days of reflux (Scheme 31).<sup>183</sup> Azidoazolopyridazines, however, yield only the imines from styrene and 2-vinylpyridine.<sup>91</sup>



R = pyrid-3-yl, pyrid-4-yl, thiophen-3-yl, isothiazol-4-yl.

SCHEME 31

The addition of aromatic sulfonyl azides to simple acyclic and cyclic dienes in a 1:2 molar ratio has been investigated.<sup>184</sup> In no case was the triazoline

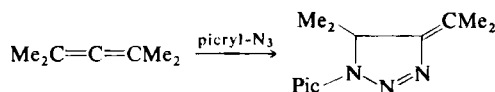
<sup>182</sup> P. K. Kadaba, *Tetrahedron* **25**, 3053 (1969).

<sup>183</sup> H. P. Figeys and R. Jamar, *Tetrahedron Lett.* **21**, 2995 (1980).

<sup>184</sup> R. A. Abramovitch, M. Ortiz, and S. P. McManus, *J. Org. Chem.* **46**, 330 (1981).

cycloaddition product isolated; nonconjugated dienes yielded sulfonimide products, whereas enamines were obtained from the conjugated dienes. Acyclic, conjugated dienes are slower reacting than their cyclic counterparts but more reactive than the nonconjugated dienes, the relative rate differences between the acyclic and cyclic conjugated dienes being attributed to steric factors.<sup>184</sup>

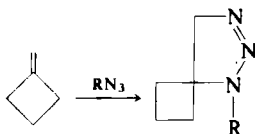
Azides add to olefins with cumulative double bonds. Tetramethylallene with picryl (pic) azide gives the stable 4-alkylidene triazoline (Scheme 32).<sup>185</sup> Although addition occurs with other azides<sup>185</sup> and other allenes,<sup>186</sup> the triazolines have not been isolated.



SCHEME 32

b. *Exocyclic Olefinic Double Bonds.* The double bonds in exocyclic olefins are unreactive and require prolonged heating, sometimes in sealed tubes, to effect azide addition. Azide reaction with exocyclic olefins provides a route for the synthesis of novel spirocyclic triazolines. Although in many cases the primary triazoline adducts are not obtained, the products of their subsequent reactions, mainly ring-expanded imines, are isolated; these are discussed in Section IV,D,2,d. Where triazoline isolation has been achieved, the yields are low.

Methylenecyclobutane and -cyclohexane undergo regiospecific azide addition to yield isolable spirotriazolines (Scheme 33).<sup>40</sup> Alkoxy carbonylmethylenecyclopropanes fail to yield the primary adduct with phenyl azide,<sup>173</sup> but unsubstituted methylene- and benzyldienecyclopropanes give a single isolable triazoline.<sup>170a,172</sup>



R = *p*-BrPh, 16 days, 50°C, sealed tube, 13%

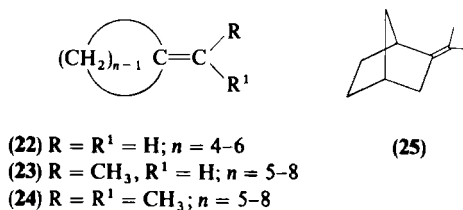
R = *p*-NO<sub>2</sub>Ph, 6 weeks, room temperature, 43%

SCHEME 33

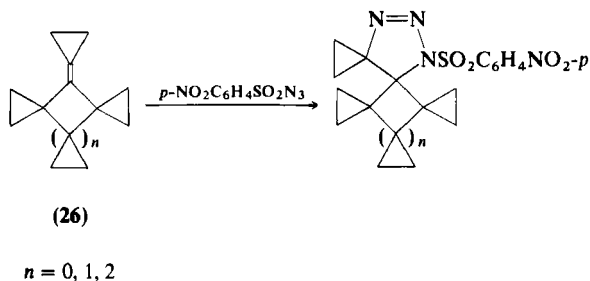
<sup>185</sup> R. F. Bleiholder and H. Schechter, *J. Am. Chem. Soc.* **90**, 2131 (1968).

<sup>186</sup> S. Borresen and J. K. Crandall, *J. Org. Chem.* **41**, 678 (1976).

Reaction of *p*-nitrobenzenesulfonyl azide with alkylidenecycloalkanes **22**–**25**<sup>187</sup> does not yield isolable triazolines as expected, but the reaction products derived from alkenes **22** and **23** suggest a single triazoline intermediate, whereas in the case of tetrasubstituted derivative **24** both possible reaction modes are present,<sup>187</sup> owing to weak double bond dissymmetry. Product analysis from **25** indicates some conflict between electronic and steric control in the addition, but provides evidence that electronic factors are much more important than steric effects in controlling regioselectivity.<sup>187</sup> Reaction of the exocyclic olefins **22** and **23** appears to be controlled more by the interaction of the LUMO of the azide and the HOMO of the alkene.<sup>187</sup> *p*-Nitrobenzenesulfonyl azide is reported to react with members of the novel



spirocyclic series **26** in a regioselective addition (Scheme 34),<sup>188,189</sup> perhaps resulting from electronic and steric influences of the spirocyclic rings.



SCHEME 34

Single, transient triazoline intermediates are also considered to be formed in the reactions of methylenecycloalkanes with cyanogen azides,<sup>190–192</sup> although again, cyclopropylidenecyclohexane gives rise to a mixture of the regioisomeric triazoline intermediates.<sup>191</sup>

<sup>187</sup> S. P. McManus, M. Ortiz, and R. A. Abramovitch, *J. Org. Chem.* **46**, 336 (1981).

<sup>188</sup> L. Fitjer, *Angew. Chem., Int. Ed. Engl.* **15**, 763 (1976).

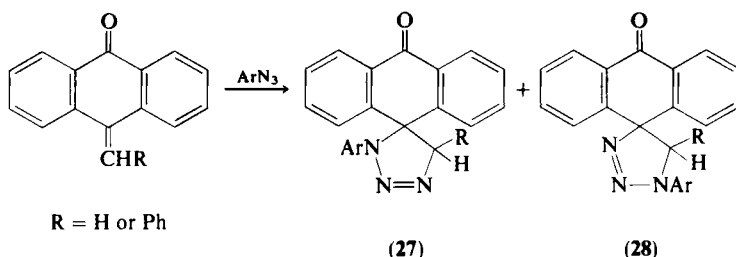
<sup>189</sup> L. Fitjer, *Chem. Ber.* **115**, 1047 (1982).

<sup>190</sup> J. E. McMurry, *J. Am. Chem. Soc.* **91**, 3676 (1969).

<sup>191</sup> J. E. McMurry and A. P. Coppolino, *J. Org. Chem.* **38**, 2821 (1973).

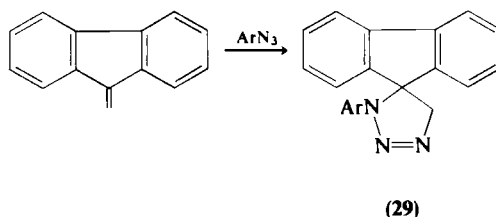
<sup>192</sup> R. A. Wohl, *J. Org. Chem.* **38**, 3862 (1973).

Quinone methides react with aryl azides (Scheme 35) to give the corresponding spiroanthonetriazolines **27** along with thermolysis products derived from the quinone methides and the triazoline.<sup>193</sup> The homogeneity and gross structure of the spiroanthonetriazolines are supported by their NMR spectra. The assignment of structure **27** rather than the regioisomeric **28** is based mainly on the acid-catalyzed enlargement products, and thus **28** cannot be rigorously excluded. 10-Benzylideneanthrone yields the spirotriazolines with phenyl azide and its 4-methyl and 4-methoxy derivatives, but not with the chloro- or nitrophenyl azides; with these only the secondary reaction products are obtained. The rate of thermal decomposition of these spirotriazolines exceeds their rate of formation and thus precludes their isolation.



SCHEME 35

In an analogous manner, 9-methylene- and 9-benzylidenefluorenes react with excess aryl azides to give spirofluorentriazolines (**29**) in 25–56% yields (Scheme 36); with *p*-nitrophenyl azide, only the ring-enlargement product is obtained.<sup>194</sup>



SCHEME 36

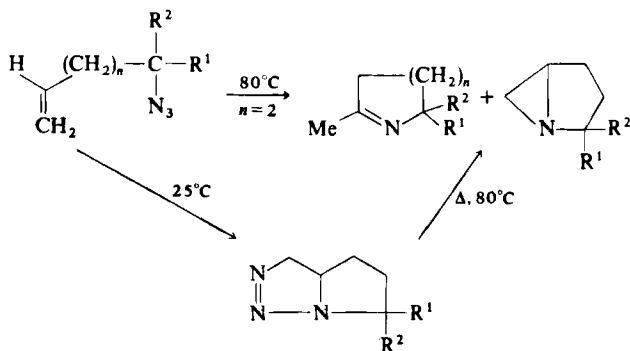
*c. Intramolecular Olefin-Azide Additions.* When the alkene and the azide moieties are suitably placed in appropriate geometric proximity within the

<sup>193</sup> K. Hirakawa, T. Ito, Y. Okubo, and S. Nakazawa, *J. Org. Chem.* **45**, 1668 (1980).

<sup>194</sup> K. Hirakawa and Y. Tanabiki, *J. Org. Chem.* **47**, 280 (1982).

same molecule, they undergo intramolecular cycloadditions to form annelated triazoline ring systems.<sup>195</sup> The range of synthetic possibilities opened by intramolecular cycloadditions for the construction of 1,5-fused triazolines is very large indeed.

Based on results presented in Scheme 37, Logothetis suggested that the thermal decomposition products from the olefinic azides in the scheme are derived from triazoline intermediates formed by an intramolecular cycloaddition reaction and not by fragmentation of the azido group to a nitrene.<sup>100</sup> However, allyl azide and 4-azido-1-pentene do not undergo internal cycloaddition because of the strain in the corresponding triazoline; they fail to give aziridines and imines upon thermolysis.<sup>100</sup>



SCHEME 37

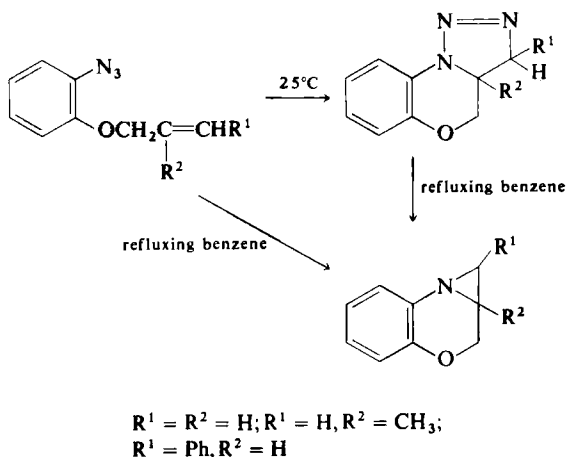
The facile decomposition of aryl azides bearing *o*-allyloxy substituents to give aziridines also involves a triazoline intermediate formed by intramolecular cycloaddition (Scheme 38).<sup>196</sup> Monitoring the reaction progress at room temperature by NMR showed, in addition to the starting azide and the final product, signals corresponding to the triazoline.

The results have been corroborated by further studies of *o*-(allyloxy)phenyl azide and 14 derivatives substituted on the allyl group. The allyloxy azide in Scheme 39 underwent complete conversion to triazoline at 35°C in 3 weeks as indicated by NMR.<sup>197</sup> Thermolysis of *o*-allylphenyl azides, on the other hand, required high temperatures of the order of 155–200°C, apparently suggesting nitrene insertion reactions.<sup>197</sup> The higher rate of decomposition of ortho-substituted phenyl azides as compared to the corresponding meta or para isomers, noted primarily in those systems where the ortho substituents have

<sup>195</sup> A. Padwa, *Angew. Chem., Int. Ed. Engl.* **15**, 123 (1976).

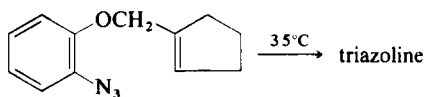
<sup>196</sup> R. Fusco, L. Garanti, and G. Zecchi, *J. Org. Chem.* **40**, 1906 (1975).

<sup>197</sup> P. A. S. Smith and S. P. Chou, *J. Org. Chem.* **46**, 3970 (1981).



SCHEME 38

some type of  $\alpha,\beta$  unsaturation, is also attributed to the concurrent formation and decomposition of a cyclic intermediate via a concerted mechanism. Those azides that thermolyze with more difficulty are thought to form discrete nitrenes in the rate-determining step.<sup>198</sup>



SCHEME 39

Several vinyl azides containing a  $\pi$  bond in close proximity to the azide functionality (**30**) have been found to undergo smooth intramolecular 1,3-dipolar cycloaddition in competition with azirine formation; the isolation of triazoline in Scheme 40 is the first example of an intramolecular cycloaddition of a vinyl azide.<sup>199-201</sup> Unlike the azidoalkenes of Logothetis, which required prolonged reaction periods for cyclization,<sup>100</sup> vinyl azides **30** are highly reactive inasmuch as the attachment of a phenyl group to the  $\pi$  system raises the HOMO and lowers the LUMO energy levels of the olefin.<sup>200</sup> The high degree of order present in the transition state as well as the interplay of

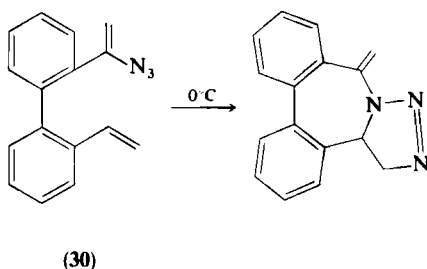
<sup>198</sup> L. K. Dyllal and J. E. Kemp, *J. Chem. Soc., B*, 976 (1968).

<sup>199</sup> A. Padwa, A. Ku, H. Ku, and A. Mazzu, *Tetrahedron Lett.*, 551 (1977).

<sup>200</sup> A. Padwa, A. Ku, H. Ku, and A. Mazzu, *J. Org. Chem.* **43**, 66 (1978); A. Padwa, H. Ku, and A. Mazzu, *ibid.*, 381.

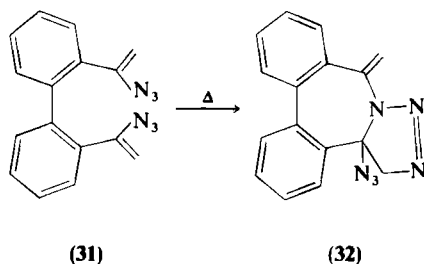
<sup>201</sup> H. Ku, *Diss. Abstr. Int. B* **41**, 2183 (1980).

favorable entropy and enthalpy factors in this system also contribute to facilitate the rate of cycloaddition.<sup>200</sup>



SCHEME 40

Vinyl azide intramolecular cycloaddition is further illustrated by the formation of azidotriazoline **32** as a minor product in the thermolysis of the bisvinyl azide **31** (Scheme 41).<sup>200</sup> An analogy is provided by the formation of 2,5-diphenylpyrrole from the slow decomposition of  $\alpha$ -azidostyrene.<sup>202</sup> Pyrrole formation is interpreted in terms of cycloaddition of the azide onto the electron-rich double bond of a second molecule to give a triazoline that loses nitrogen and rearranges to a pyrroline followed by hydrogen azide elimination (Section IV,D).<sup>203</sup>



SCHEME 41

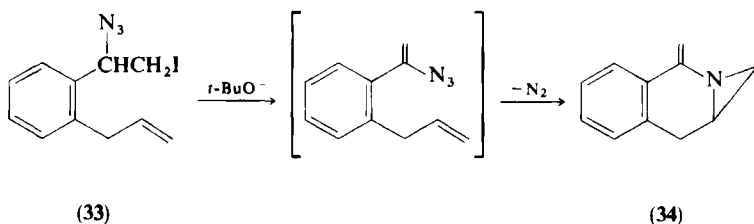
The formation of **34** from **33** in the reaction of Scheme 42 is explained by a rapid intramolecular cycloaddition of the initially formed vinyl azide followed by loss of nitrogen.<sup>200</sup>

The azide band in the IR spectrum of the vinyl azide in Scheme 43 disappears after 18 hours at room temperature and a crystalline triazoline is obtained.<sup>204</sup>

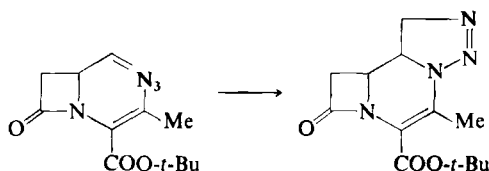
<sup>202</sup> J. H. Boyer, W. E. Krueger, and R. Modler, *Tetrahedron Lett.*, 5979 (1968).

<sup>203</sup> G. L'abbé, *Angew. Chem., Int. Ed. Engl.* **14**, 775 (1975).

<sup>204</sup> M. J. Pearson, *Chem. Commun.*, 947 (1981).

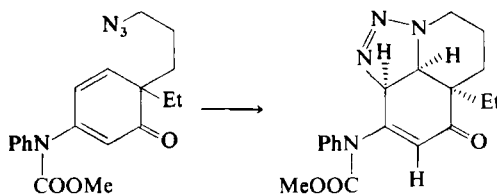


**SCHEME 42**



**SCHEME 43**

The azidodienone yields a triazoline (Scheme 44) in refluxing benzene solution, apparently via an azide-olefin intramolecular cycloaddition.<sup>205</sup>



**SCHEME 44**

### 3. *Electron-Rich Double Bonds*

Conjugated electron-releasing substituents in enamines and enol ethers highly activate the olefin. Enamines attain a  $10^6$ -fold increase in reaction rate over conjugated alkenes<sup>26,28,39</sup> and illustrate the importance of the electron density at the double bond. Exceptional reactivity has been reported for enamines<sup>30,37,38</sup> and enol ethers,<sup>26</sup> although enol ethers are inferior to enamines. Azide addition is unidirectional and stereospecific<sup>26</sup>; it is controlled by electronic rather than steric factors,<sup>26,28,37,135</sup> and the amino or ether group always appears in the 5-position of the triazoline

<sup>205</sup> A. G. Schultz and C. K. Sha, *J. Org. Chem.* **45**, 2041 (1980).

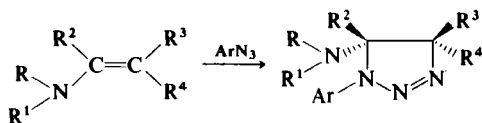


ring.<sup>15,26,31,35,37,39,206</sup> The same orientation rules apply to aryl as well as to acyl azides such as azidoformates and imidoyl azides.<sup>31,35</sup> Reactions are most effective with azides bearing electron-withdrawing groups,<sup>28,42</sup> although with tosyl and phosphoryl azides the triazolines are never isolated; they undergo *in situ* thermolysis and lead to amidines or aromatize spontaneously to triazoles (Section IV,A and D,2,e,f). However, triazolines derived from cyclic enamines and enol ethers fail to give triazoles.<sup>39</sup>

The reactivity and regioselectivity of azide addition to enamines and enol ethers are explained by the FMO theory<sup>51</sup>; the dominant interaction is HOMO<sub>olefin</sub>–LUMO<sub>azide</sub> controlled, and because the terminal azide nitrogen and the olefinic carbon not bearing the amino or ether function have the larger coefficient in the LUMO and HOMO, respectively, the electron-donor groups always appear at C-5 of the triazoline adducts.<sup>135,207</sup> The vinylic ethers are less reactive than the enamines because they have larger ionization potentials, and thus HOMO<sub>enol ether</sub> < HOMO<sub>enamine</sub>.<sup>51</sup>

a. *Enamines*. The “N-4 compounds” obtained by Alder from heating a mixture of cyclooctene and phenyl azide (Scheme 49) are perhaps the first examples of 5-aminotriazolines.<sup>43–45</sup>

Triazolines obtained by the addition of aryl azides to enamines are generally isolable and a considerable number of triazoline compounds have been prepared in this way (Scheme 45).<sup>208,209</sup> Although usually nitrophenyl azide is used, because electron-withdrawing groups on the azide facilitate addition,<sup>28,42</sup> diethylaminophenyl azide also works satisfactorily (Scheme 46).<sup>209</sup>



SCHEME 45

Enamines derived from a secondary amine and aldehydes or ketones, linear and cyclic, have also been shown to react with equal facility (Scheme 47).<sup>30,35,37,38,206,210–213</sup> In fact, azide addition to enamines formed *in situ*

<sup>206</sup> R. A. Abramovitch, S. R. Challand, and Y. Yamada, *J. Org. Chem.* **40**, 1541 (1975).

<sup>207</sup> L. Citerio, M. L. Saccarello, and P. Trimarco, *J. Heterocycl. Chem.* **16**, 289 (1979).

<sup>208</sup> G. Bianchetti, P. D. Croce, D. Pocar, and G. G. Gallo, *Rend. — Ist. Lomb. Accad. Sci. Lett., A* **99**, 296 (1965) [*CA* **65**, 15367a (1966)].

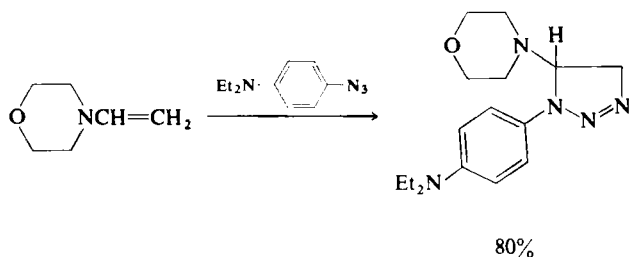
<sup>209</sup> P. Ferruti, D. Pocar, and G. Bianchetti, *Gazz. Chim. Ital.* **97**, 109 (1967).

<sup>210</sup> G. Bianchetti, D. Pocar, P. D. Croce, and A. Vigevani, *Chem. Ber.* **98**, 2715 (1965).

<sup>211</sup> G. Bianchetti, R. Stradi, and D. Pocar, *J.C.S. Perkin I*, 997 (1972).

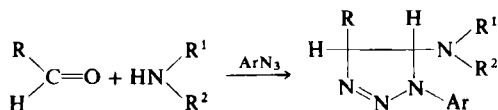
<sup>212</sup> M. de Poortere and F.C. de Schriver, *Tetrahedron Lett.*, 3949 (1970).

<sup>213</sup> J. F. Stephen and E. Marcus, *J. Heterocycl. Chem.* **6**, 969 (1969).



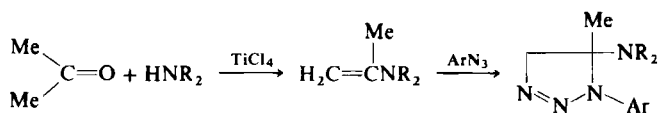
SCHEME 46

occurs under more favorable conditions than it does with isolated enamines. Aldehyde derived enamines give 1,4,5-substituted triazolines with the amino group in the 5-position (Scheme 47); with ketones, an additional substituent is present in the 5-position. Aliphatic aldehydes and aliphatic secondary amines or aralkyl amines with aryl azides give excellent yields of triazolines, but with aromatic amines yields are poor.<sup>214-216</sup> By employing thioalkyl aldehydes, 4-thioalkyl-5-aminotriazolines have been prepared.<sup>217</sup>



SCHEME 47

Titanium tetrachloride is used *in situ* as a catalyst to help form enamines from acetone and other dialkyl ketones.<sup>215</sup> 1-Aryl-5-dialkylaminotriazolines bearing at least one hydrogen at the 4-position have thus been obtained (Scheme 48).<sup>216</sup>



SCHEME 48

Aryl azides and aldehydes or ketones in the presence of ammonia or amines generally give high yields of triazolines and provide a route to triazolines with no substituents in the 5-amino group.<sup>218,219</sup>

<sup>214</sup> G. Bianchetti, D. Pocar, P. D. Croce, and R. Stradi, *Gazz. Chim. Ital.* **97**, 304 (1967).

<sup>215</sup> R. Stradi and D. Pocar, *Gazz. Chim. Ital.* **99**, 1131 (1969).

<sup>216</sup> R. Stradi, D. Pocar, and G. Bianchetti, *Org. Magn. Reson.* **4**, 247 (1972).

<sup>217</sup> G. Bolis, D. Pocar, R. Stradi, and P. Trimarco, *J.C.S. Perkin I*, 2365 (1977).

<sup>218</sup> C. E. Olsen, *Acta Chem. Scand.* **28**, 425 (1974).

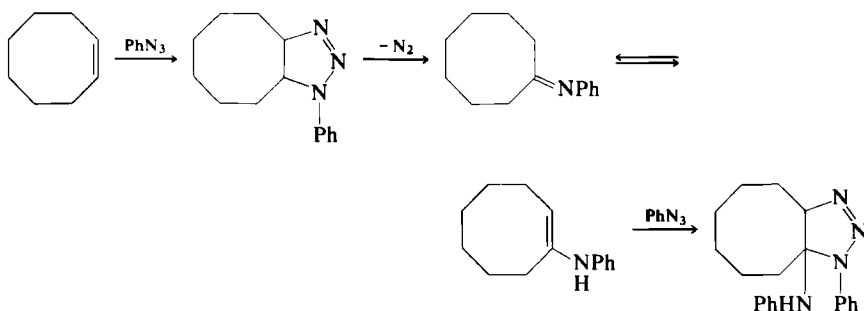
<sup>219</sup> H. Wamhoff and P. Sohar, *Chem. Ber.* **104**, 3501 (1971).

Heterocyclic azides react with enamines<sup>31</sup>; 1,8-naphthyridine azides give isolable triazolines.<sup>220</sup> The bicyclic enamine 2-*N*-morpholinonornbornene with aryl and benzoyl azides furnishes stable, crystalline aminotriazolines.<sup>39,213</sup> Likewise, alkyl azidoformates yield stable triazolines.<sup>30,221</sup>

1-Azidoadamantane fails to react with enamines (see Scheme 18).<sup>155</sup> The FMO of phenyl azide and 1-azidoadamantane suggests that the latter may be as reactive as phenyl azide toward electron-poor dipolarophiles but less reactive toward electron-rich dipolarophiles because of its relatively higher LUMO energy.<sup>155</sup>

Both  $\alpha$ - and  $\beta$ -styryl azides undergo regioselective addition to enamines to provide 1-vinyl-5-aminotriazolines in moderate yields.<sup>222</sup> 1-Pyrrolidinyl enamines react with  $\alpha$ -styryl azide more readily than piperidino or morpholino enamines;  $\beta$ -styryl azide is as reactive as phenyl azide,  $\alpha$ -styryl azide less so.<sup>222</sup>

Although azides cannot undergo addition to imines (Schiff bases),<sup>16,214</sup> when the possibility of imine–enamine tautomerism exists, reaction occurs with the enamine to yield 5-aminotriazolines.<sup>35,43,81,180,208,214,223–226</sup> In fact, Alder's N-4 compounds were obtained as shown in Scheme 49.



SCHEME 49

Enamines are also obtained *in situ* from  $\alpha,\beta$ -unsaturated aldehydes and secondary amines.<sup>227,228</sup> With aryl azides, the two possible stereoisomers are

<sup>220</sup> O. Livi, E. Amato, G. Biagi, P. L. Ferrarini, and G. P. Primofiore, *Farmaco, Ed. Sci.* **33**, 838 (1978).

<sup>221</sup> R. E. Thomas, *Diss. Abstr. Int. B* **36**, 728 (1975).

<sup>222</sup> Y. Nomura, Y. Takeuchi, S. Tomoda, and M. M. Ito, *Bull. Chem. Soc. Jpn.* **54**, 261 (1981).

<sup>223</sup> G. Bianchetti, P. D. Croce, and D. Pocar, *Tetrahedron Lett.*, 2043 (1965).

<sup>224</sup> G. Bianchetti, P. D. Croce, D. Pocar, and A. Vigevani, *Gazz. Chim. Ital.* **97**, 289 (1967).

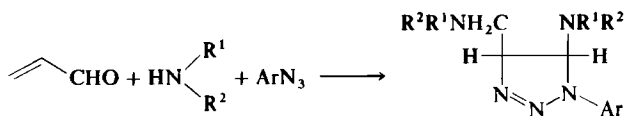
<sup>225</sup> R. D. Burpitt and V. W. Goodlett, *J. Org. Chem.* **30**, 4308 (1965).

<sup>226</sup> A. C. Ritchie and M. Rosenberger, *J. Chem. Soc. C*, 227 (1968).

<sup>227</sup> D. Pocar, R. Stradi, and L. M. Rossi, *J.C.S. Perkin I*, 619 (1972).

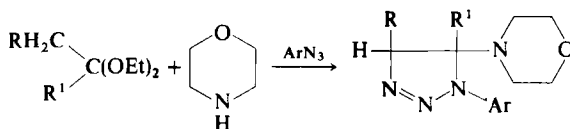
<sup>228</sup> D. Pocar, R. Stradi, and L. M. Rossi, *J.C.S. Perkin I*, 769 (1972).

produced in equimolar quantities, as established by NMR spectroscopy. Similar results are obtained using cyclic secondary amines, and the reaction provides a route to 4-aminoalkyl-5-alkylaminotriazolines (Scheme 50).<sup>227</sup> The two diastereomers are separated by base deamination to triazoles because triazolines are deaminated at different rates.  $\alpha,\beta$ -Unsaturated aldehydes and thiols, in the presence of secondary amines and aryl azides, give the 4-thioalkyl-5-aminotriazoline.<sup>217</sup>



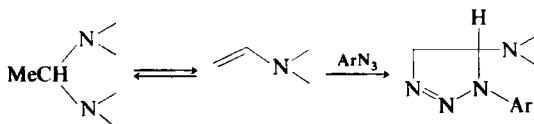
SCHEME 50

Other methods for generating enamines *in situ* include the action of secondary amines on acetals (Scheme 51)<sup>229,230</sup> or Schiff bases<sup>231</sup>; the yields of 5-aminotriazolines are, however, modest.



SCHEME 51

Azide addition to enamines may be employed to shift amine–enamine equilibria (Scheme 52).<sup>209</sup>



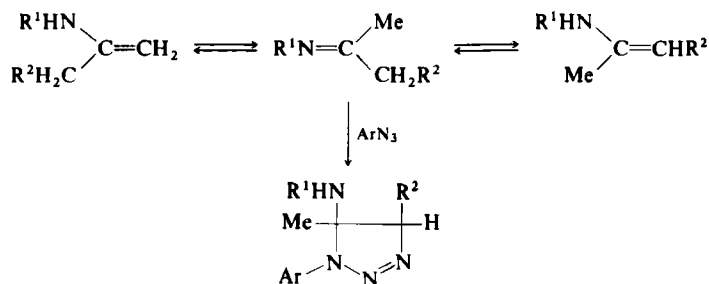
SCHEME 52

Mixtures of triazolines are obtained from enamines in which tautomerism is possible, although generally the major product results from the more stable enamine (Scheme 53).<sup>208,223,224</sup>

<sup>229</sup> G. Bianchetti, P. Ferruti, and D. Pocar, *Gazz. Chim. Ital.* **97**, 579 (1967).

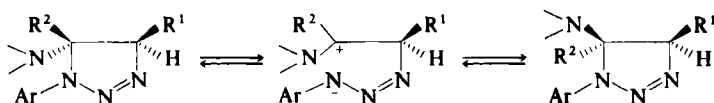
<sup>230</sup> G. Bianchetti, D. Pocar, P. D. Croce, G. G. Gallo, and A. Vigevani, *Tetrahedron Lett.*, 1637 (1966).

<sup>231</sup> D. Pocar, G. Bianchetti, and P. Ferruti, *Gazz. Chim. Ital.* **97**, 597 (1967).



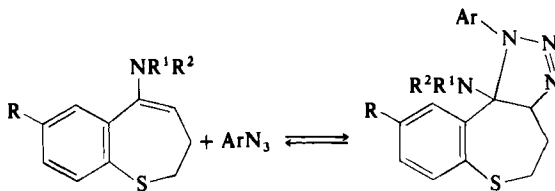
SCHEME 53

Reaction of aryl azide with *cis*-*trans* mixtures of enamines yields, under kinetically controlled conditions, only the *trans*-triazolines, as shown by NMR studies. At higher temperatures or in the presence of acid, however, the *trans*-triazoline epimerizes to give a *cis*-*trans* equilibrium mixture; the isomer ratio at equilibrium is dictated by steric repulsions in the triazoline ring, and the size of the substituents does not seem to exert a significant effect.<sup>211</sup> The proposed mechanism involves the breaking of the N-1/C-5 bond (Scheme 54), although an N-1/N-2 rupture is equally feasible.



SCHEME 54

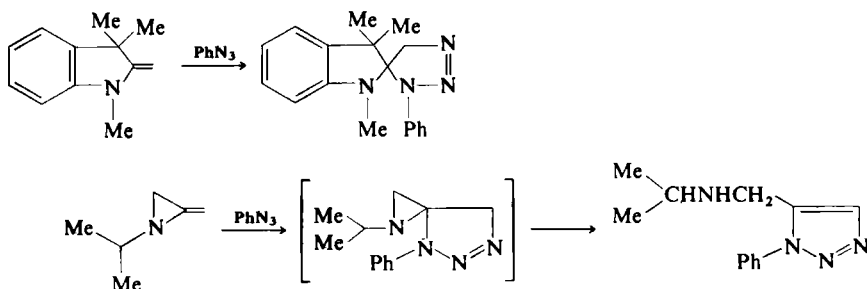
The consistently low yields in the cycloaddition of aryl azides to certain enamines have been attributed to an unfavorable equilibrium between cycloaddition and cycloreversion reactions.<sup>232</sup> The reversibility of the cycloaddition has been demonstrated on the basis of spectroscopic (Section III) and chemical evidence (Scheme 55). The conditions for cycloaddition and cycloreversion have been examined, using MO calculations.<sup>72</sup>



SCHEME 55

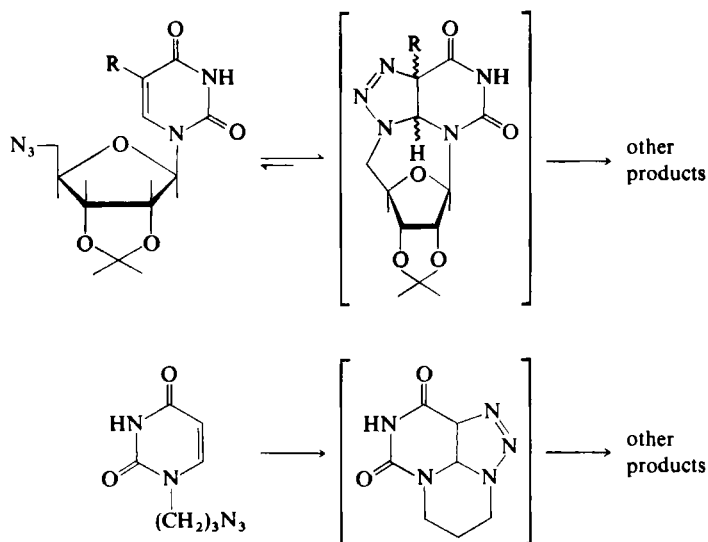
<sup>232</sup> L. M. Rossi and P. Trimarco, *J. Heterocycl. Chem.* 17, 1545 (1980).

The exocyclic olefinic bond in strained enamines can undergo cycloaddition with aryl azides to give spirotriazoline adducts that are stable<sup>233</sup> or that spontaneously isomerize to triazoles (Section IV,A) (Scheme 56).<sup>234</sup>



SCHEME 56

Labile annelated 5-aminotriazolines are also postulated as intermediates in the intramolecular reaction of the azido group with the 5,6 double bond of pyrimidines (Scheme 57).<sup>235,236</sup>



SCHEME 57

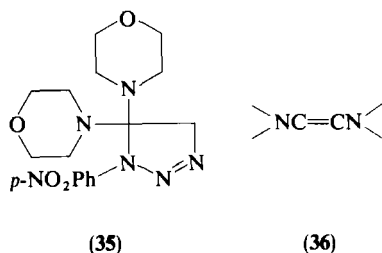
<sup>233</sup> M. Regitz and G. Himbert, *Justus Liebigs Ann. Chem.* **734**, 70 (1970).

<sup>234</sup> J. K. Crandall, L. C. Crawley, and J. B. Komin, *J. Org. Chem.* **40**, 2045 (1975).

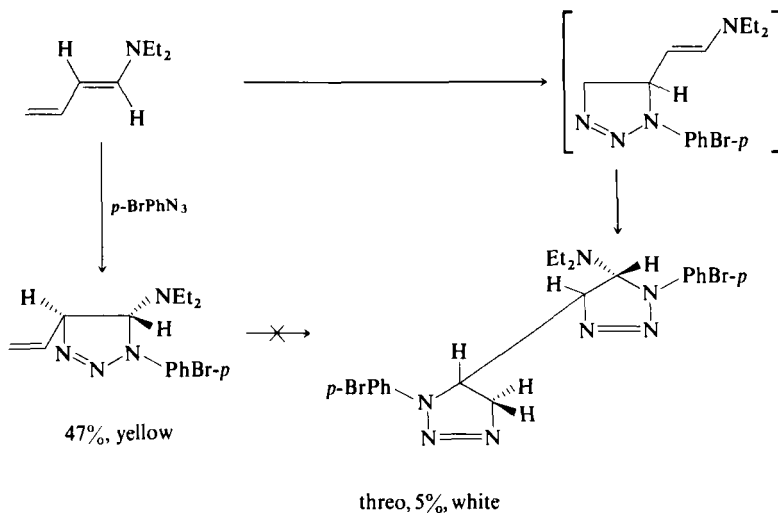
<sup>235</sup> T. Sasaki, K. Minamoto, T. Suzuki, and T. Sugiura, *J. Org. Chem.* **44**, 1424 (1979).

<sup>236</sup> T. Sasaki, K. Minamoto, T. Suzuki, and S. Yamashita, *Tetrahedron* **36**, 865 (1980).

b. *Enediamines*. Very little research has been done in this area; triazoline adducts from the reaction of aryl azides and enediamines are usually unstable, and only one case is known where isolation of the triazoline **35** has been achieved.<sup>216</sup> Ethylene-1,2-diamines **36**, with aryl azides, lead to rearrangement products derived from thermolysis of the intermediate triazolines.<sup>207,237</sup> The regiospecificity of the cycloaddition is determined by product analysis and MO considerations.<sup>207</sup>



c. *Dienamines*. The work in this area has been fragmentary; depending on the nature of the substituent, the monoadduct **37**<sup>230</sup> or a mixture of the mono- and diadducts<sup>238</sup> or products of thermolysis<sup>239</sup> are obtained. In Scheme 58,



SCHEME 58

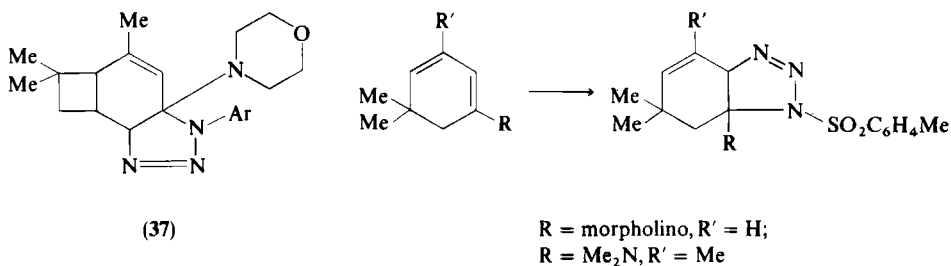
<sup>237</sup> J. Bourgois and F. Texier, *C. R. Hebd. Seances Acad. Sci., Ser. C* **284**, 509 (1977).

<sup>238</sup> H. Cardoen, S. Toppet, G. Smets, and G. L'abbé, *J. Heterocycl. Chem.* **9**, 971 (1972).

<sup>239</sup> D. Pocar, G. Bianchetti, and P. D. Croce, *Gazz. Chim. Ital.* **95**, 1220 (1965).

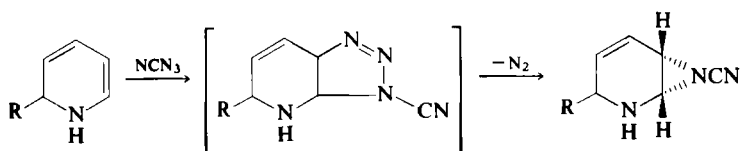
the bistriazoline is formed from the intermediate monotriazoline enamine, which, because of its high reactivity, cannot be isolated; the olefinic bond in the 5-aminotriazoline is not reactive enough for further azide addition to occur. Spectroscopic data strongly suggest a threo configuration for the bistriazoline (Section III,B,4).<sup>238</sup>

The first isolation of a 5-amino-1-tosyltriaazoline from the action of tosyl azide on a cyclic dienamine at low temperature has been reported recently (Scheme 59).<sup>240</sup>



SCHEME 59

Both 1,2-<sup>241,242</sup> and 1,4-dihydropyridines<sup>243</sup> behave as enamines rather than as dienes<sup>244</sup> in cycloaddition reactions; with azides bearing electron-withdrawing groups, they provide a route for the preparation of bicycloaziridines in quantitative yields via thermolysis of the intermediate triazolines (Scheme 60).<sup>241,242</sup> The reactions of dienamines have been reviewed.<sup>245</sup>



SCHEME 60

d. *Enamino Esters and Nitriles.* The dipolarophilic activity of enamines is reduced by the introduction of an electron-withdrawing group.<sup>57</sup> The triazolines resulting from amino esters, ketones, and nitriles are stable

<sup>240</sup> D. Pocar, M. C. Ripamonti, R. Stradi, and P. Trimarco, *J. Heterocycl. Chem.* **14**, 173 (1977).

<sup>241</sup> T. A. Ondrus, E. E. Knaus, and C. S. Giam, *J. Heterocycl. Chem.* **16**, 409 (1979).

<sup>242</sup> T. A. Ondrus, E. E. Knaus, and C. S. Giam, *Can. J. Chem.* **57**, 2342 (1979).

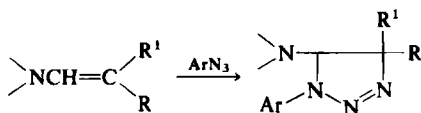
<sup>243</sup> B. K. Warren and E. E. Knaus, *J. Med. Chem.* **24**, 462 (1981).

<sup>244</sup> B. Weinstein, L.-C. Chang Lin, and F. W. Fowler, *J. Org. Chem.* **45**, 1657 (1980).

<sup>245</sup> O. Cervinka and A. Fabryova, *Chem. Listy* **70**, 1266 (1976).



when  $R^1$  is methyl<sup>135</sup>; when  $R^1$  is hydrogen, the triazolines are never isolated because spontaneous aromatization to triazole occurs by expulsion of a molecule of amine (Scheme 61).<sup>239,246–248</sup> Triazoline adducts from  $\alpha$ -aminoacrylonitriles lose a molecule of hydrogen cyanide in preference to the amine.<sup>249</sup> Aryl azide reaction with  $\alpha$ - and  $\beta$ -aminoacrylonitriles indicates stereoselective addition, with the amino group always appearing at the 5-position.<sup>135,249</sup> The enamino esters and nitriles do not behave as acrylic derivatives but as enamines; the reactions are controlled by LUMO<sub>azide</sub>–HOMO<sub>olefin</sub> interaction and the log of cycloaddition rates is linearly related to the inverse of the azide LUMO-olefin HOMO energy gaps.<sup>135,249</sup>



$R = \text{COOR, COR, CN}$

$R^1 = \text{H, Me}$

SCHEME 61

The *trans*-triazolines in Scheme 61 ( $R^1 = \text{CH}_3$ ) epimerize to *cis*-*trans* mixtures similar to triazolines derived from simple enamines (Section II,A,3,a). This results from triazoline cycloreversion<sup>250</sup> and the isomerization of the enamino compounds thus formed.<sup>135,250</sup>

*e. Enol Ethers.* The addition of aryl azides to open-chain and cyclic enol ethers leading to 5-alkoxytriazolines has been studied extensively.<sup>26,39</sup> Depending on the substituents, a mixture of triazoline and its thermolysis product, the imino ether, is obtained (Scheme 62). The imino ether is the only product when the  $\beta$  carbon of the vinylic ether is fully substituted,<sup>174</sup> whereas triazoline formation predominates when no substituents are present.<sup>39</sup> When there is only a single substituent on the  $\beta$  carbon, a mixture is obtained in which the imino ether is the major component.<sup>174</sup> Cyclic vinylic ethers yield only the triazolines.<sup>39,251,252</sup>

<sup>246</sup> R. Fusco, G. Bianchetti, D. Pocar, and R. Ugo, *Gazz. Chim. Ital.* **92**, 1040 (1962).

<sup>247</sup> R. Fusco, G. Bianchetti, D. Pocar, and R. Ugo, *Chem. Ber.* **96**, 802 (1963).

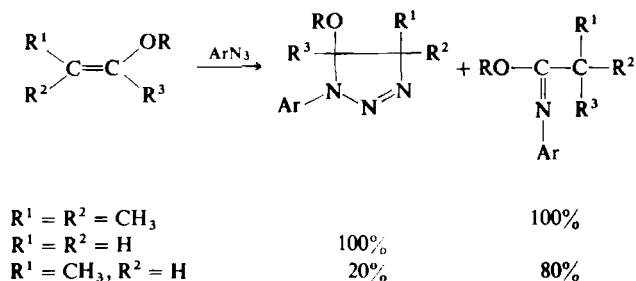
<sup>248</sup> S. Maiorana, D. Pocar, and P. D. Croce, *Tetrahedron Lett.*, 6043 (1966).

<sup>249</sup> F. Texier, A. Derdour, H. Benhaoua, T. Benabdellah, and O. Yebdri, *Tetrahedron Lett.* (23), 1893 (1982).

<sup>250</sup> F. Texier and J. Bourgois, *J. Heterocycl. Chem.* **12**, 505 (1975).

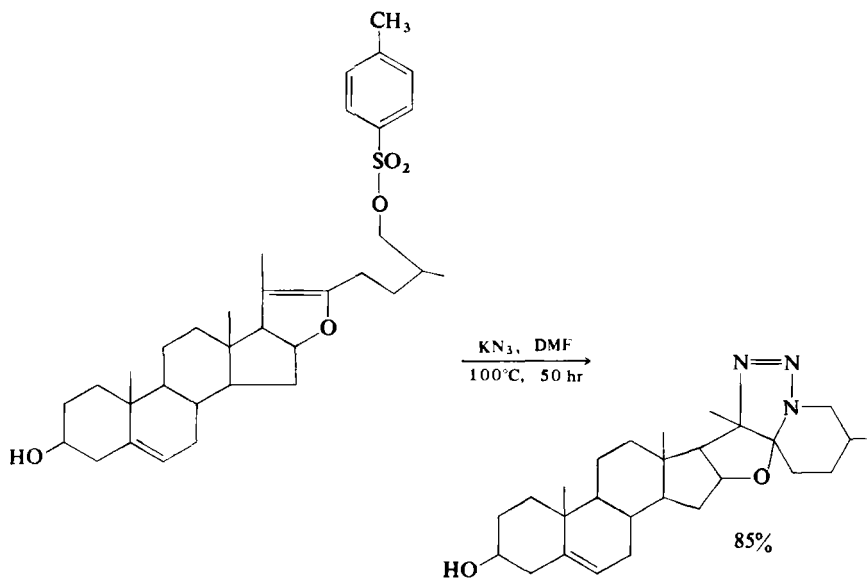
<sup>251</sup> B. Green and D. W. Liu, *Tetrahedron Lett.*, 2807 (1975).

<sup>252</sup> P. Scheiner, *J. Org. Chem.* **32**, 2022 (1967).



SCHEME 62

An example of intramolecular azide addition to the olefinic bond of an enol ether is provided by the synthesis of a heptacyclic steroidal triazoline (Scheme 63).<sup>253</sup> The dipolar aprotic solvent that is used is considered to facilitate the cycloaddition.<sup>11,182</sup>



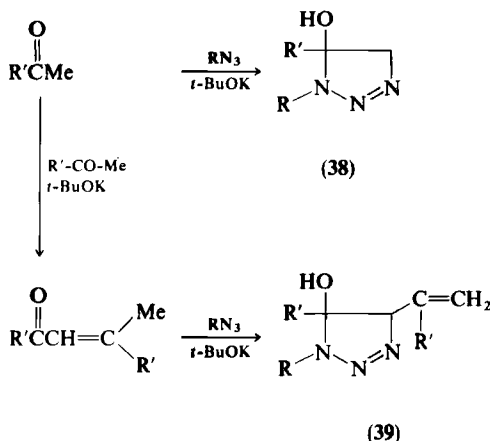
SCHEME 63

Orientation of azide addition to allenic ethers is nonspecific; addition occurs preferentially to the activated double bond in the  $\beta,\gamma$ -position to the oxygen atom.<sup>254</sup>

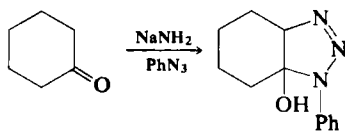
<sup>253</sup> F. C. Uhle, *J. Org. Chem.* **32**, 1596 (1967).

<sup>254</sup> P. Battioni, L. Vo-Quang, and Y. Vo-Quang, *Bull. Soc. Chim. Fr.*, 415 (1978).

f. *Enolizable Ketones*. Enolizable ketones, in the presence of a strong base, undergo cycloaddition with azides to give 5-hydroxytriazolines,<sup>255-259</sup> which under the reaction conditions yield triazoles or other reaction products (Section IV). Methyl ketones lead to complex mixtures in which the two triazoline adducts **38** and **39** have been identified (Scheme 64).<sup>255</sup> Cyclic ketones also yield triazolines (Scheme 65).<sup>260</sup>



SCHEME 64



SCHEME 65

1-Alkyl- and 1-aryl-5-hydroxytriazolines with two different substituents at C-4 exist in solution as an equilibrium mixture of two diastereomers,<sup>261,262</sup> apparently as a result of the conversion of the triazoline to open-chain

<sup>255</sup> C. E. Olsen, *Acta Chem. Scand.* **27**, 1987 (1973).

<sup>256</sup> C. E. Olsen, *Angew. Chem., Int. Ed. Engl.* **13**, 349 (1974).

<sup>257</sup> C. E. Olsen and C. Pedersen, *Tetrahedron Lett.*, 3805 (1968).

<sup>258</sup> C. E. Olsen and C. Pedersen, *Acta Chem. Scand.* **27**, 2271 (1973).

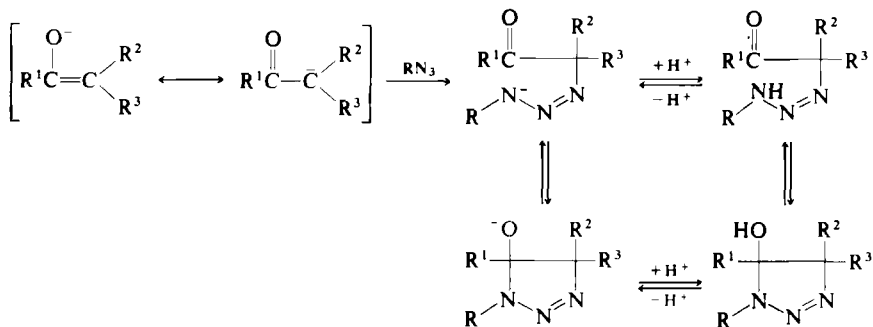
<sup>259</sup> C. E. Olsen and C. Pedersen, *Acta Chem. Scand.* **27**, 2279 (1973).

<sup>260</sup> H. Krieger and M. Sodervall, *Suomen Kemistil. B* **40**, 294 (1967).

<sup>261</sup> C. E. Olsen, *Acta Chem. Scand.* **27**, 2983 (1973).

<sup>262</sup> C. E. Olsen, *Acta Chem. Scand., Ser. B* **29** 953 (1975).

triazenes in solution,<sup>259,261,262</sup> analogous to that observed in 5-amino-triazolines (Scheme 54).<sup>211</sup> The anions of the 5-hydroxytriazolines can also exist in the closed or open form, depending on the substituents.<sup>263</sup> The various experimental observations thus lead to a unifying scheme for the reactions of organic azides with enolizable carbonyl compounds (Scheme 66).<sup>263</sup>



SCHEME 66

Azide addition to enolizable ketones is regiospecific and may be considered as a 1,3-dipolar cycloaddition occurring at the double bond of the enolate, similar to the addition of azides to electron-rich olefins. However, a stepwise reaction appears more probable because glycosyl azides exhibit anomerism when they react with activated methylene compounds, thus indicating the presence of a triazene intermediate.<sup>264</sup> On the other hand, the formation of the triazene intermediate may be considered as a limited case of 1,3-dipolar cycloaddition where one of the bonds is formed completely before the other one starts,<sup>2</sup> such a limited case being observed for the Diels–Alder reaction.<sup>265</sup>

g. *Ketene Acetals*. Although early attempts to isolate triazoline adducts from ketene acetals and azides were unsuccessful,<sup>266,267</sup> by proper control of reaction temperature in the presence of excess acetal, isolation has now been achieved (Scheme 67).<sup>268,269</sup> Mono- and disubstituted ketene acetals react in an analogous fashion.<sup>268–271</sup>

<sup>263</sup> C. E. Olsen, *Acta Chem. Scand.* **27**, 2989 (1973).

<sup>264</sup> R. L. Tolman, C. W. Smith, and R. K. Robins, *J. Am. Chem. Soc.* **94**, 2530 (1972).

<sup>265</sup> R. Gompper, *Angew. Chem., Int. Ed. Engl.* **8**, 312 (1969).

<sup>266</sup> P. Grunanger, P. Vita-Finzi, and E. Fabbri, *Gazz. Chim. Ital.* **90**, 413 (1960).

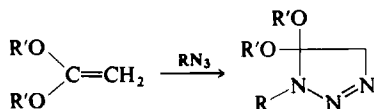
<sup>267</sup> R. Scarpati, D. Sica, and A. Lionetti, *Gazz. Chim. Ital.* **93**, 90 (1963).

<sup>268</sup> M. L. Graziano and R. Scarpati, *J. Heterocycl. Chem.* **13**, 205 (1976).

<sup>269</sup> R. Scarpati, M. L. Graziano, and R. A. Nicolaus, *Gazz. Chim. Ital.* **98**, 681 (1968).

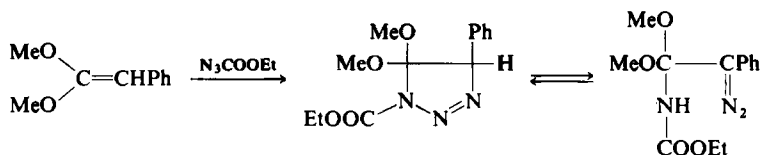
<sup>270</sup> R. Scarpati, M. L. Graziano, and R. A. Nicolaus, *Gazz. Chim. Ital.* **100**, 665 (1970).

<sup>271</sup> R. Scarpati and D. Sica, *Gazz. Chim. Ital.* **93**, 942 (1963).



SCHEME 67

The triazoline resulting from the addition of ethyl azidoformate to phenylketene dimethylacetal at  $-15^\circ\text{C}$  for two months has been shown to exist in equilibrium with the isomeric diazo compound (Scheme 68).<sup>272,273</sup>



SCHEME 68

By contrast, phenyl azide and tetramethoxyethylene yield only the products of the triazoline thermolysis.<sup>274,275</sup>

#### 4. Electron-Poor Double Bonds

Olefinic double bonds substituted with one or more electron-withdrawing groups show significant dipolarophilic activity in cycloaddition reactions with organic azides,<sup>43,276–278</sup> similar to the electron-rich double bonds of enamines and enol ethers; the reactivity is less pronounced in azide additions compared to that observed in diazomethane reactions.<sup>7</sup> The first triazolines reported resulted by the action of aryl azides on benzoquinones.<sup>1,279–281</sup> As a rule, stereospecific *cis* additions occur,<sup>32</sup> which are usually unidirectional except in the case of methacrylic derivatives<sup>67</sup> and certain alkenes bearing

<sup>272</sup> R. Scarpati and M. L. Graziano, *Tetrahedron Lett.*, 4771 (1971).

<sup>273</sup> R. Scarpati and M. L. Graziano, *J. Heterocycl. Chem.* **9**, 1087 (1972).

<sup>274</sup> R. W. Hoffmann, U. Bressel, J. Gehlhaus, H. Hauser, and G. Muhl, *Chem. Ber.* **104**, 2611 (1971).

<sup>275</sup> R. W. Hoffmann and H. Hauser, *Tetrahedron Lett.*, 1365 (1964).

<sup>276</sup> T. Curtius and K. Raschig, *J. Prakt. Chem.* **125**, 466 (1930).

<sup>277</sup> S. M. Gurvich and A. P. Terentev, *Sb. Statei Obshch. Khim.* **1**, 409 (1953) [*CA* **49**, 1047 (1955)].

<sup>278</sup> N. G. Khusainova, Z. A. Bredikhina, F. K. Karataeva, T. I. Bychkova, and A. N. Pudovik, *Zh. Obshch. Khim.* **46**, 1712 (1976).

<sup>279</sup> L. Wolff, *Justus Liebigs Ann. Chem.* **399**, 274 (1913).

<sup>280</sup> F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.* **127**, 1307 (1925); 113 (1926).

<sup>281</sup> L. Fieser and J. L. Hartwell, *J. Am. Chem. Soc.* **57**, 1479 (1935).

three electron-withdrawing substituents.<sup>282</sup> The orientation of addition is controlled by electronic factors, with the terminal azido nitrogen attacking the more nucleophilic center in the olefin. Thus the products are 1,4- or 1,4,5-substituted triazolines with the electron-withdrawing group always appearing at the 4-position, and the latter orientation dominates even where addition occurs in both directions.<sup>67</sup> The reaction is facilitated by electron-donating substituents on the azide component,<sup>28</sup> the reactivity order being the reverse of that observed with enamines and enol ethers.<sup>17</sup>

In terms of the FMO theory,<sup>63</sup> the favored interaction is  $\text{HOMO}_{\text{azide}} - \text{LUMO}_{\text{olefin}}$ , in contrast to that observed in electron-rich olefins. Bond formation occurs between the substituted azido nitrogen and the olefinic carbon not bearing the electron-withdrawing group because these have the larger coefficients; this accounts for the appearance of the electron-withdrawing substituent in the 4-position. The Hammett  $\rho$  values of  $-1.1$  and  $-0.8$  for maleic anhydride and *N*-phenylmaleimide, respectively,<sup>28</sup> are in agreement with the direction of charge transfer indicated by  $\text{HOMO}_{\text{azide}} - \text{LUMO}_{\text{olefin}}$  interactions.

a. *Alkenes Bearing One Electron-Withdrawing Group.* Cycloaddition reactions of aryl and alkyl azides with alkenes bearing an electron-withdrawing group and a free  $\alpha$  hydrogen are highly regioselective and lead to 1,4-substituted triazolines<sup>32,67,278</sup> or to the isomeric diazo compounds (Scheme 69).<sup>67,283,284</sup> Representative examples are presented in Table I. Triazolines bearing electron-withdrawing groups at the 4-position have been shown to isomerize readily to ring-opened diazo compounds under the influence of a base<sup>32</sup> in an equilibrium reaction that resembles the Dimroth rearrangement

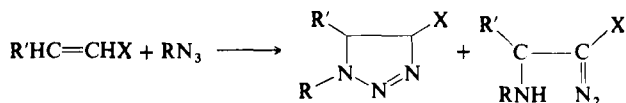
TABLE I  
EXAMPLES OF AZIDE ADDITION TO ELECTRON-POOR OLEFINS  
BEARING ONE ELECTRON-WITHDRAWING GROUP (SCHEME 69)

R	R'	X	Triazoline/ diazo compound (%)	Reference
Ph	H	COOMe	100/0	32
Ph	H	P(O)(OR) <sub>2</sub>	100/0	278
Ph	H	COMe	0/100	32
Ph	Me	COOMe	0/100	32
Ph	Ph	COOMe	0/100	284

<sup>282</sup> M. S. Ouali, M. Vaultier, and R. Carrie, *Tetrahedron* **36**, 1821 (1980).

<sup>283</sup> O. Livi, P. L. Ferrarini, D. Bertini, and I. Tonetti, *Farmaco, Ed. Sci.* **30**, 1017 (1975).

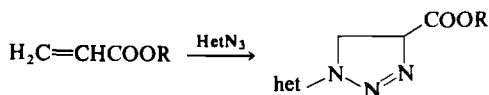
<sup>284</sup> F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 3642 (1971).



SCHEME 69

in the triazole series.<sup>285</sup> In some cases the diazo compound reacts further with the excess alkene and gives rise to pyrazolines.<sup>32,283</sup>

Although 1,8-naphthyridine azide with methyl acrylate gives only pyrazolines,<sup>283</sup> other heterocyclic azides afford triazolines as the sole products with acrylic esters (see, e.g., in Scheme 70).<sup>286,287</sup>

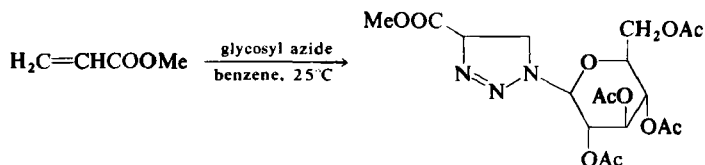


R = CH<sub>3</sub> or Et

het = 5- or 6-azido-2-methylbenzothiazole

SCHEME 70

Glycosyl azides and methyl acrylate give triazoline nucleoside in modest yield (Scheme 71).<sup>288</sup>



32%

SCHEME 71

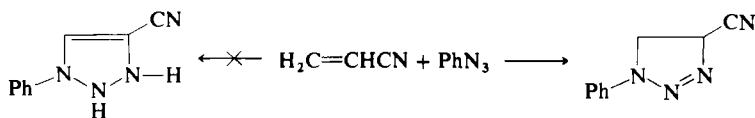
The assignment of a  $\Delta^4$ -triazoline structure<sup>277</sup> for the product obtained from the reaction of acrylonitrile and phenyl azide appears highly unlikely, because later work indicates this adduct to have an unambiguous 1-aryl-4-cyano- $\Delta^2$ -1,2,3-triazoline structure (Scheme 72).<sup>32</sup> Likewise, vinyl phosphonates react with phenyl azide, leading to triazoline-4-phosphonates.<sup>278</sup>

<sup>285</sup> O. Dimroth, *Justus Liebigs Ann. Chem.* **335**, 1 (1905); **338**, 143 (1905); **373**, 336 (1910); B. R. Brown, D. L. Hammick, and S. G. Heritage, *J. Chem. Soc.*, 3820 (1953).

<sup>286</sup> I. A. Ol'shevskaya and O. A. Brazhnik, *Ukr. Khim. Zh.* **47**, 861 (1981) [*CA* **95**, 203814c (1981)].

<sup>287</sup> I. A. Ol'shevskaya, *Khim. Geterotsikl. Soedin.*, 839 (1982).

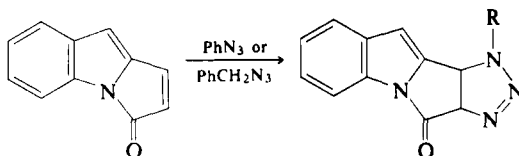
<sup>288</sup> M. T. Garcia-Lopez, G. Garcia-Munoz, and R. Madronero, *J. Heterocycl. Chem.* **9**, 717 (1972).



SCHEME 72

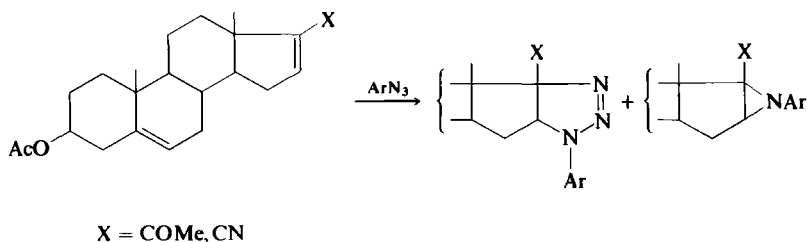
The reactivity and regioselectivity of 1-azidoadamantane (See Scheme 18), a bridgehead azide, have been investigated with electron-poor olefins.<sup>155</sup> The reaction with ethyl acrylate proceeds smoothly at 25°C to afford exclusively the 4-substituted triazoline in good yield; the regiochemistry is supported by <sup>13</sup>C- and <sup>1</sup>H-NMR spectral data.  $\beta$ -Nitrostyrene and nitroethylene give only triazoles.

Several triazolines have been derived from pyrrolinones in an approach to build the tetracyclic framework present in mitomycin antibiotics (Scheme 73).<sup>289,290</sup>



SCHEME 73

Azide addition also occurs with the electron-poor olefinic double bond in androstene; a mixture of the triazoline adduct and aziridine is obtained, the latter arising from the thermolysis of the triazoline formed by azide addition in the opposite direction (Scheme 74).<sup>251</sup>



SCHEME 74

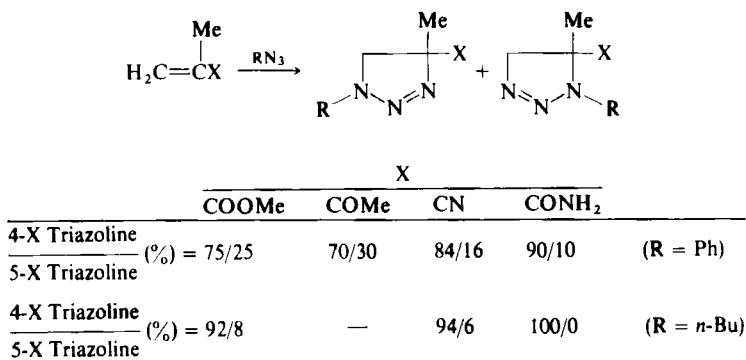
Azide addition to methacrylic esters, ketones, nitriles, and amides (Scheme 75),<sup>32,67</sup> lacks the high regioselectivity observed when no  $\alpha$ -methyl substituent is present (refer to Scheme 69); the 4-substituted triazoline always

<sup>289</sup> R. W. Franck and J. Auerbach, *J. Org. Chem.* **36**, 31 (1971).

<sup>290</sup> G. J. Siuta, R. W. Franck, and R. J. Kempton, *J. Org. Chem.* **39**, 3739 (1974).



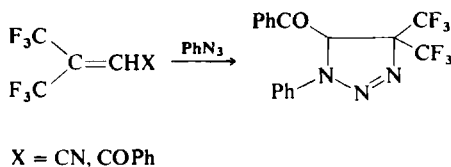
predominates.<sup>67</sup> The regioselectivity is greater with alkyl azides than with aryl azides; *n*-butyl azide gives only the 4-substituted product with methacrylamide (Scheme 75). The 4-substituted triazolines undergo thermolysis at much lower temperatures than the isomeric 5-substituted compounds, which are stable up to 100°C or higher.<sup>67</sup>



SCHEME 75

$\alpha$ -Bromoacrylic esters appear to undergo regioselective addition with both alkyl and aryl azides to give stable 4-bromo-substituted triazolines that undergo dehydrohalogenation only under the influence of heat or a base.<sup>291</sup>

Addition of phenyl azide to olefins bearing trifluoromethyl groups appears to be anomalous, the electron-withdrawing substituent being in the 5- rather than in the 4-position of the triazoline (Scheme 76).<sup>292</sup>



SCHEME 76

Olefins bearing other electron-withdrawing groups react with organic azides to give triazolines of varying stability<sup>89,155,293–296</sup>; they undergo

<sup>291</sup> Japanese Kokai Tokyo Koho Patent 81, 127, 363 (1981) [CA 96, P85593a (1982)].

<sup>292</sup> Y. M. Saunier, R. Danion-Bougot, D. Danion, and R. Carrie, *Tetrahedron* 32, 1995 (1976).

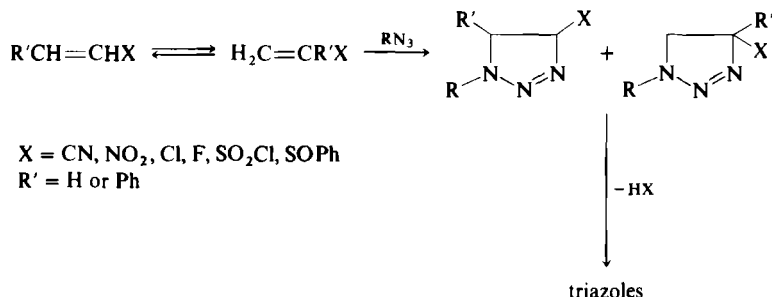
<sup>293</sup> C. S. Rondestvedt and P. K. Chang, *J. Am. Chem. Soc.* 77, 6532 (1955).

<sup>294</sup> G. Rembarz, B. Kirchhoff, and G. Dongowski, *J. Prakt. Chem.* 33, 199 (1966).

<sup>295</sup> P. D. Callaghan and M. S. Gibson, *Chem. Commun.*, 918 (1967).

<sup>296</sup> J. S. Meek and J. S. Fowler, *J. Org. Chem.* 33, 985 (1968); N. S. Zefirov and N. K. Chapovskaya, *Zh. Org. Khim.*, 1300 (1968); 2596 (1970); N. S. Zefirov, N. K. Chapovskaya, and V. V. Kolesnikov, *Chem. Commun.*, 1001 (1971).

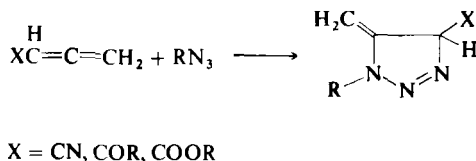
spontaneous aromatization to triazoles by eliminating a stable fragment (Scheme 77). The mixture of isomeric triazoles often formed is believed to arise from azide addition in both directions,<sup>294,295</sup> although an olefin isomerization in the reaction medium has also been suggested (Section IV,A,3,c).<sup>297</sup>



SCHEME 77

Sodium azide also reacts with olefins of the type shown in Scheme 77 to give triazoles through the intermediacy of triazolines.<sup>295,296,298,299</sup> The mechanism involving nucleophilic displacement of the substituent X by azide ion, followed by cyclization of the vinyl azide,<sup>295</sup> does not seem to apply because neutral vinyl azides fail to cyclize.<sup>300</sup>

Allenic ketones and esters are found to react with azides by addition, preferentially to the activated double bond in the  $\alpha,\beta$ -position to the ester or keto group, although no regioselectivity is observed.<sup>254</sup> Allenic nitriles undergo similar additions, and unstable methylene triazolines are obtained (Scheme 78).<sup>301</sup>



SCHEME 78

There are also examples of azide addition to exocyclic as well as to intramolecular electron-poor double bonds. The reaction of phenyl azide with

<sup>297</sup> See refs. 90 and 92 to unpublished work in ref. 2.

<sup>298</sup> S. Maiorana, *Ann. Chim. (Rome)* **56**, 1531 (1966) [*CA* **67**, 32420 (1967)].

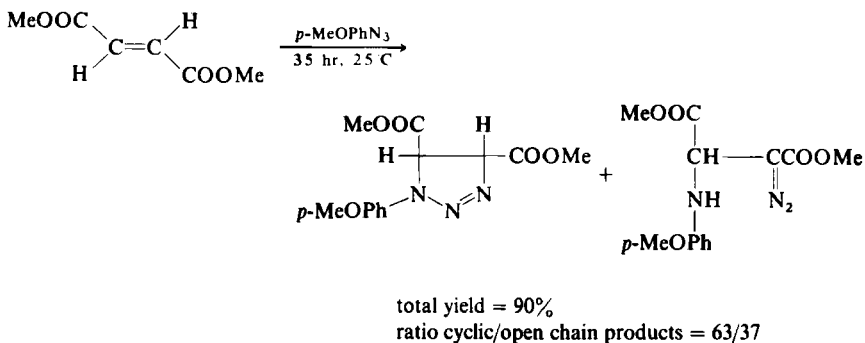
<sup>299</sup> A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk. SSSR* **167**, 109 (1966) [*CA* **64**, 17578 (1966)]; Y. Tanaka and S. I. Miller, *J. Org. Chem.* **37**, 3370 (1972).

<sup>300</sup> F. P. Woerner and H. Reimlinger, *Chem. Ber.* **103**, 1908 (1970).

<sup>301</sup> W. Ried and H. Mengler, *Justus Liebigs Ann. Chem.* **678**, 95 (1964).

several 2-alkoxycarbonylmethylenecyclopropanes yields triazoles from the intermediate triazoline adducts (Section IV,A,1).<sup>173</sup> Unstable pyrrolotriazolines are obtained from the intramolecular cycloaddition reactions of both *cis-cis* and *trans-cis* 3-substituted 6-azidohexa-2,4-dienoate esters, the rate of addition depending on the ester stereochemistry and substitution.<sup>302</sup> The stereoelectronic effects in the intramolecular 1,3-dipolar addition of substituted  $\omega$ -azido- $\alpha,\beta$ -unsaturated esters have also been explored in connection with approaches to the synthesis of antitumor-active bisperidylpiperazinediones.<sup>303</sup>

b. *Alkenes Bearing Two or More Electron-Withdrawing Groups.* The chemical behavior of olefins substituted with two vicinal electron-withdrawing groups is similar to that of acrylic derivatives.<sup>32,304</sup> Thus the addition of an alkyl or aryl azide to dimethyl fumarate gives a mixture of the triazoline and the corresponding diazo compound (Scheme 79).<sup>32</sup>



SCHEME 79

As expected, azide addition to dimethyl maleate is very sluggish, and a triazoline is not isolated<sup>32</sup> because the  $\text{LUMO}_{\text{fumarate}} < \text{LUMO}_{\text{maleate}}$ .<sup>304a</sup> Recently, however, it has been found that azide coordinated in a cobalt chelate complex  $[\text{N}_3\text{Co}(\text{DH})_2\text{NH}_3]$  is sufficiently reactive to add to diethyl maleate, and 25% of the pure triazoline has been obtained (Scheme 80).<sup>305</sup>

Fumaric and maleic dinitriles react similarly, but the 4,5-dicyanotriazolines formed *in situ* lose a molecule of hydrogen cyanide and give a triazole with the

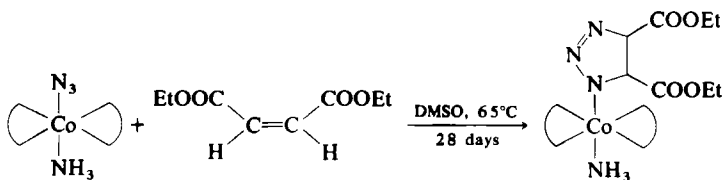
<sup>302</sup> R. J. Sundberg and B. C. Pearce, *J. Org. Chem.* **47**, 725 (1982).

<sup>303</sup> V. A. Piermattie, *Diss. Abstr. Int. B* **40**, 5678 (1980) [CA **93**, 71710n (1980)].

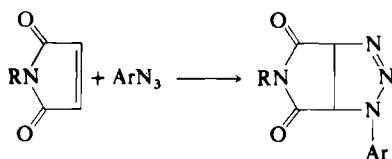
<sup>304</sup> E. Van Loock, G. L'abbé, and G. Smets, *J. Org. Chem.* **36**, 2520 (1971).

<sup>304a</sup> O. Eisenstein and N. T. Anh, *Bull. Soc. Chim. Fr.*, 2721 (1973).

<sup>305</sup> T. Kemmerich, J. H. Nelson, N. E. Takach, H. Boehme, B. Jablonski, and W. Beck, *Inorg. Chem.* **21**, 1226 (1982).



SCHEME 80



SCHEME 81

remaining cyano group in the 4-position.<sup>32,306</sup> Likewise, azidoazolopyridazines, with fumaric and maleic esters, give labile triazoline adducts that lose nitrogen to yield enamines.<sup>91</sup>

Stable triazolines are obtained from aryl azides and  $N$ -alkyl and  $N$ -aryl maleimides (Scheme 81)<sup>307–309a</sup>; the reaction succeeds with silyl azides<sup>310</sup> and is utilized in the synthesis of polymers from bisazides and bismaleimides.<sup>311,312</sup> Unlike maleimides, maleic anhydrides do not yield stable triazolines; with trimethylsilyl azide the reaction products are oxazinediones (Section IV,A).<sup>310,313,314</sup>

In its reaction toward aryl azides,  $N$ -phenylmaleimide is found more active than maleic anhydride with rate constants for phenyl azide addition at  $25^\circ\text{C}$  being 72 and  $2.8 \times 10^{-6}$ , respectively,<sup>28</sup> although on the basis of orbital donor–acceptor interactions between dipoles and dipolarophiles, the reverse should be the case.<sup>315</sup> Such anomalies can be explained by taking into consideration not only orbital donor–acceptor interactions but also localization energies; thus maleic anhydride with a higher localization energy than  $N$ -phenylmaleimide is the less reactive of the two.<sup>315</sup>

<sup>306</sup> P. K. Kadaba, *J. Heterocycl. Chem.* **13**, 1153 (1976); P. K. Kadaba and J. Triplett, *Heterocycles* **9**, 243 (1978).

<sup>307</sup> A. Mustafa, S. M. A. D. Zayed, and S. Khattab, *J. Am. Chem. Soc.* **78**, 145 (1956).

<sup>308</sup> W. I. Awad, S. M. A. R. Omran, and F. Nagieb, *Tetrahedron* **19**, 1591 (1963).

<sup>309</sup> S. J. Davis and C. S. Rondstvedt, *Chem. Ind. (London)*, 845 (1956).

<sup>309a</sup> P. K. Kadaba, unpublished results.

<sup>310</sup> S. S. Washburne, W. R. Peterson, Jr., and D. A. Berman, *J. Org. Chem.* **37**, 1738 (1972).

<sup>311</sup> Y. Gilliams and G. Smets, *Makromol. Chem.* **117**, 1 (1968).

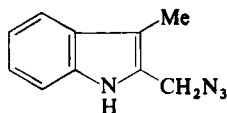
<sup>312</sup> Y. Gilliams and G. Smets, *Makromol. Chem.* **128**, 263 (1969).

<sup>313</sup> J. D. Warren, J. H. MacMillan, and S. S. Washburne, *J. Org. Chem.* **40**, 743 (1975).

<sup>314</sup> J. H. MacMillan and S. S. Washburne, *J. Heterocycl. Chem.* **12**, 1215 (1975).

<sup>315</sup> Ya. D. Samuilov, A. I. Movchan, and A. I. Konovalov, *Zh. Obshch. Khim.* **50**, 447 (1980).

Heterocyclic azides such as 2-azidomethylindoles (40) are also reported to react successfully with *N*-phenyl- and *N*-methylmaleimides to give high yields of the triazoline adducts.<sup>316</sup>



(40)

SCHEME 82

In a search for cytostatic quinones, both benzoquinones and naphthoquinones have been treated with glycosyl azides; labile *N*-glycosyl triazolines are formed, which aromatize to triazoles or lose nitrogen to give enamines.<sup>317</sup>

The reaction of phenyl azide with 1,2-dibenzoyl ethylene is more complex; the various thermolysis products (Section IV, A,3,c and D,2,g) clearly indicate the intermediacy of a 4,5-dibenzoyl triazoline.<sup>306</sup>

The polycondensation of 4,4'-diphenylene diazide with *p*-benzoquinone or ethylene dimethacrylate, leading to heat resistant oligomers containing triazoline and aziridine segments, also appears to proceed through the initial formation of triazoline rings, which later form aziridines.<sup>318</sup>

Olefins bearing two geminal electron-withdrawing groups, like the vicinally substituted alkenes, undergo cycloaddition with alkyl and aryl azides to yield stable triazolines (Scheme 83).<sup>319-322</sup> The reaction proceeds stereospecifically in one direction<sup>321</sup> with both electron-withdrawing groups appearing on the 4-position of the triazoline adduct. The azide reactivity follows the same order as for other electron-poor olefins.<sup>321</sup> When X or Y is a nitrile group, the triazoline formed from the addition of phenyl azide undergoes thermolysis *in situ* and leads to pyrrolidines.<sup>319,322</sup> However, when X or Y is a nitro group, reaction with sodium azide results in loss of nitrous acid, and a triazole is reported with the acyl group in the 5-position (Scheme 84).<sup>323</sup>

The cycloaddition of organic azides to olefins substituted by three electron-withdrawing groups can give a single triazoline, indicating a single orientation

<sup>316</sup> Y. Tamura, M. W. Chun, K. Ohno, S. Kwon, and M. Ikeda, *Chem. Pharm. Bull.* **26**, 2874 (1978).

<sup>317</sup> G. Alonso, M. Fuertes, M. T. Garcia-Lopez, F. G. de las Heras, J. M. Infante, and M. Stud, *Eur. J. Med. Chem.—Chim. Ther.* **13**, 155 (1978).

<sup>318</sup> Ya. T. Pimenov, V. I. Berzin, and R. M. Livshits, *Vysokomol. Soedin., Ser. B* **16**, 132 (1974).

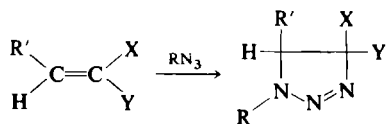
<sup>319</sup> F. Texier and R. Carrie, *Tetrahedron Lett.*, 823 (1969).

<sup>320</sup> F. Texier and R. Carrie, *C.R. Hebd. Seances Acad. Sci., Ser. C* **271**, 958 (1970).

<sup>321</sup> F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 4119 (1971).

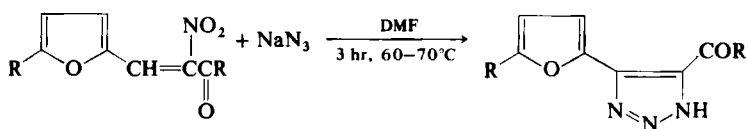
<sup>322</sup> F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 258 (1972).

<sup>323</sup> A. I. Sitkin, V. I. Klimenko, and G. Kh. Khisamutdinov, *Ukr. Khim. Zh.* **45**, 180 (1979) [*CA* **90**, 168513b (1979)].



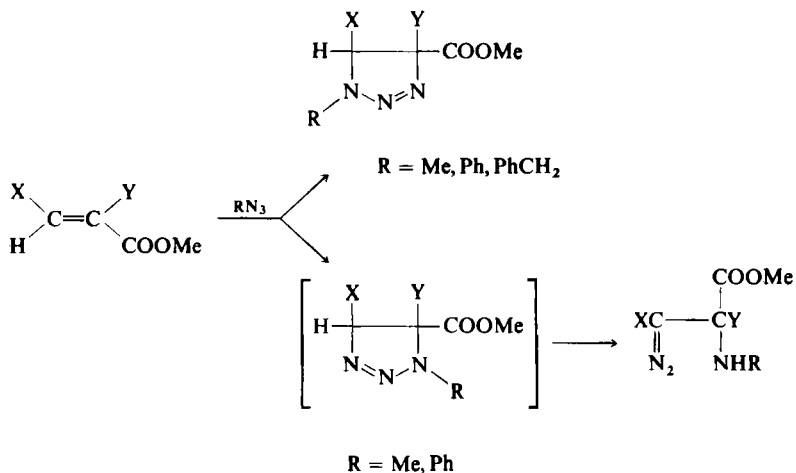
X and/or Y = COOR, COR, CN, CONH<sub>2</sub>  
 R = Me or Ph

SCHEME 83



SCHEME 84

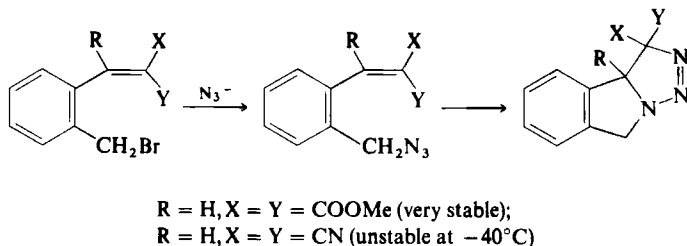
of addition. In other cases a mixture of a triazoline and a diazo compound is obtained; this points to a double orientation of addition (Scheme 85). The triazoline structures have been confirmed by <sup>13</sup>C-NMR as well as by chemical methods.<sup>282</sup>



X = COOMe, Y = CN  
 X = Y = COOMe  
 X = CN, Y = COOMe  
 X = CPh, Y = COOMe  
 X = COMe, Y = COOMe

SCHEME 85

Evidence for intramolecular 1,3-dipolar cycloaddition is presented for the reaction of styrenes geminally substituted on the olefinic bond with electron-withdrawing groups and bearing an azidomethyl substituent in the ortho position of the benzene ring (Scheme 86).<sup>324</sup> The isoindolotriazolines thus formed vary greatly in their thermal stability, depending on the substituents X, Y, and R; when R is methyl, the stability in general increases.<sup>324</sup>



SCHEME 86

## B. FROM DIAZOALKANES AND IMINES (SCHIFF BASES)

Diazoalkanes, like azides, are 1,3-dipoles of the propargyl-allenyl type (Scheme 87)<sup>15</sup> and their reaction with imines provides a route for building the triazoline framework from the C—N—N and C—N fragments. Although diazomethane addition to the carbon-carbon double bond was achieved by von Pechmann in 1898,<sup>325</sup> its reaction toward the carbon-nitrogen double bond was investigated only 50 years later.



SCHEME 87

The first attempt to add diazomethane to a Schiff base was made by Meerwein,<sup>326</sup> and the first successful addition was observed by Mustafa.<sup>327</sup> Anils bearing nitro groups on the phenyl rings gave a cyclic adduct to which a 1,2,4-triazoline structure was assigned.<sup>327</sup> A later reexamination of the reaction established the correct orientation of addition, and the products of the reaction of diazomethane with Schiff bases were assigned a  $\Delta^2$ -1,2,3-

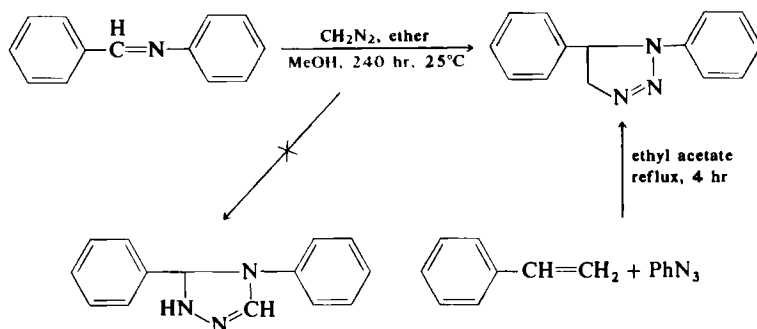
<sup>324</sup> P. Kolsaker, P. O. Ellingsen, and G. Woien, *Acta Chem. Scand., Ser. B* **B32**, 683 (1979).

<sup>325</sup> H. von Pechmann, *Chem. Ber.* **31**, 2950 (1898).

<sup>326</sup> H. Meerwein, *Angew. Chem.* **60**, 78 (1948).

<sup>327</sup> A. Mustafa, *J. Chem. Soc.*, 234 (1949).

triazoline structure based on their identity with adducts obtained from the phenyl azide–styrene reaction (Scheme 88).<sup>34</sup> The catalytic effect of small amounts of methanol was also illustrated during this study.<sup>34</sup>



SCHEME 88

Diazomethane addition to Schiff bases is regiospecific and controlled by electronic rather than steric factors; only a single triazoline adduct is formed, as evidenced by kinetic<sup>328</sup> and spectral data (Section III).<sup>329</sup> Diazoalkane addition to imines occurs under mild conditions and is a versatile route to the synthesis of 1,5-substituted triazolines because a wide range of substituents can be incorporated into the imine component.<sup>329–331</sup> Imines derived from both aldehydes and ketones react, including aliphatic, aromatic, and heterocyclic Schiff bases. The use of substituted diazoalkanes in the synthesis of 1,4,5-substituted triazolines offers great potential but has not been explored fully. However, the reaction of diazonitriles with benzalanilines has been investigated.<sup>332</sup> Selective reviews that briefly cover reactions of diazo compounds<sup>333</sup> and the chemistry of silyldiazo compounds,<sup>334</sup> diazomethane,<sup>335</sup> and other diazoalkanes<sup>336,337</sup> have been published.

<sup>328</sup> P. K. Kadaba and J. O. Edwards, *J. Org. Chem.* **26**, 2331 (1961).

<sup>329</sup> P. K. Kadaba, *J. Heterocycl. Chem.* **12**, 143 (1975).

<sup>330</sup> P. K. Kadaba, *Tetrahedron* **22**, 2453 (1966).

<sup>331</sup> P. K. Kadaba and N. F. Fannin, *J. Heterocycl. Chem.* **4**, 301 (1967).

<sup>332</sup> F. Roelants and A. Bruylants, *Tetrahedron* **34**, 2229 (1978).

<sup>333</sup> H. Hertel, *Ullmanns Encykl. Tech. Chem.*, 4. Aufl. **10**, 109 (1975) [*CA* **88**, 120105b (1978)].

<sup>334</sup> A. Sekiguchi and W. Ando, *Yuki Gosei Kagaku Kyokaiishi* **35**, 897 (1977) [*CA* **88**, 121259s (1978)].

<sup>335</sup> T. H. Black, *Aldrichim. Acta* **16**, 3 (1983); H. B. Hopps, *ibid.* **3**, No. 4, 9 (1970).

<sup>336</sup> M. Regitz, in "The Chemistry of Diazonium and Diazo Groups" (S. Patai, ed.), p. 659. Wiley (Interscience), New York, 1978; D. S. Wulman, G. Linstrumelle, and C. F. Cooper, *ibid.*, p. 821.

<sup>337</sup> M. Regitz, "Diazoalkanes—Properties and Synthesis," Thieme, Stuttgart, 1977.

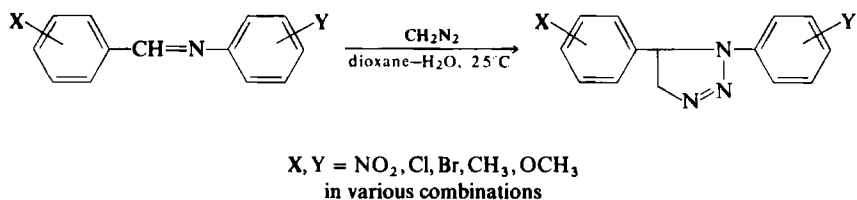


The diazomethane–imine addition can be interpreted in terms of the FMO theory.<sup>51</sup> Calculations on diazoalkanes and benzyldeneanilines lead to two orbital interactions, a  $\text{HOMO}_{\text{diazoalkane}}\text{--LUMO}_{\text{imine}}$  and a  $\text{LUMO}_{\text{diazoalkane}}\text{--HOMO}_{\text{imine}}$ , but regardless of which one is the favored interaction, the coefficients of the atomic orbitals of the bonding atoms favor the formation of a 1,2,3- and not a 1,2,4-triazoline.<sup>338</sup> And indeed, the 1,2,4-triazolines proposed by Mustafa<sup>327</sup> have never been observed.

The addition of diazoalkanes to alkenes and alkynes has been shown to be a  $\text{HOMO}_{\text{diazoalkane}}\text{--LUMO}_{\text{dipolarophile}}$  controlled reaction,<sup>51,53</sup> and because the orbital energies of imines are comparable to those of electron-poor olefins, the reactivity of diazoalkanes toward imines may also be considered a  $\text{HOMO}_{\text{diazoalkane}}\text{--LUMO}_{\text{imine}}$  favored interaction.<sup>338</sup>

### 1. Arylideneanilines

The reaction of diazomethane with benzalanilines (Scheme 89) has been investigated in detail; kinetic studies indicate that the reaction involves a nucleophilic attack by the diazomethane carbon on the Schiff-base carbon in a bimolecular cycloaddition reaction of second order. As in other dipolar cycloadditions, a significant substituent effect is present and electron-withdrawing groups favor the reaction.<sup>182,328,330</sup> This is as expected from the orbital interpretation of the addition; electron-withdrawing groups will lower the imine LUMO and increase its reactivity by reducing the HOMO–LUMO energy differences of the reactants.



SCHEME 89

The cycloaddition of diazomethane to benzalanilines does not show any pronounced solvent effect; with increasing dielectric constant of the solvent, there is hardly any increase in reaction rate with the exception of protic (e.g., water, alcohols) and dipolar aprotic solvents (e.g., DMF) that produce a significant acceleration in the reaction rate.<sup>182</sup> The protic–dipolar aprotic solvent effects are found to be dependent on the electron-withdrawing or

<sup>338</sup> See ref. 165 to unpublished work in ref. 2.

-releasing nature of the substituents on the phenyl rings, the influence of substituents on the *N*-phenyl being greater than those on the *C*-phenyl. These observations have been rationalized by a mechanism involving negative charge stabilization on the Schiff-base nitrogen in the transition state; in the absence of an electron-withdrawing group, the negative charge is more localized, and solvation by protic solvents through hydrogen bonding interactions dominates. Charge delocalization by electron-withdrawing groups decreases solvation through hydrogen bonding and increases solvation by dipolar aprotic solvents through polarizability interactions,<sup>182</sup> based on the mutual polarizability of solvent and solute molecules.<sup>339</sup> Numerous examples of similar solvent effects in cycloaddition reactions have been pointed out, and a general explanation based on transition state stabilization through solvation effects has been offered.<sup>11,182</sup>

In terms of the FMO theory, one approach considers the solvation phenomenon as a donor-acceptor type of interaction between solvent and reagents, and the protic-solvent effect in the reaction of diazomethane with benzalanilines is explained as resulting from a favorable decrease in the HOMO-LUMO energy differences of the reactants.<sup>338</sup> In another approach, a two-step mechanism compatible with experimental observations on stereoselectivity, substituent, and solvent effects is derived from semiempirical MINDO/3 calculations, according to which the reaction passes through two transition states separated by an intermediate, the solvation being greater in the second transition state and maximum in the intermediate.<sup>73</sup> Solvation calculations indicate that as the dielectric constant of the solvent medium increases, so does the charge transfer, and the energy profile is stabilized. Thus the solvent effect is analogous to the one produced by the introduction of a substituent that reinforces the normal charge transfer. The effect of the first transition state, where the first  $\sigma$  bond is being formed, is very slight, which is in agreement with the weak effect of solvent polarity on rate.<sup>73</sup> It appears likely that in the second transition state and in the intermediate, the increased charge transfer would lead to increased electronic polarizability, which in turn would result in increased polarizability interactions with DMF. In the absence of electron-withdrawing groups, charge transfer would be decreased, and hydrogen-bonding interactions become more important.

The accelerating effect of protic solvents on the cycloaddition of diazomethane to Schiff bases has been used to advantage in devising an ingenious reaction procedure for the general synthesis, in high yield, of 1,5-substituted 1,2,3-triazolines.<sup>11,182,329-331</sup> The diazomethane reagent for the addition is prepared from nitrosomethylurea, using *p*-dioxane in place of the

<sup>339</sup> A. J. Parker, *Q. Rev., Chem. Soc.* **16**, 163 (1962); *Adv. Phys. Org. Chem.* **5**, 173 (1967); *Adv. Org. Chem.* **1**, 1 (1965); *Chem. Rev.* **69**, 1 (1969).

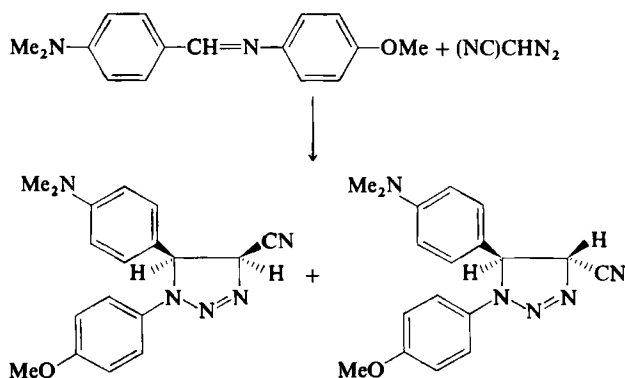
conventional diethyl ether,<sup>340</sup> and the wet diazomethane solution containing sufficient water to catalyze the reaction is used directly.<sup>330</sup> Earlier attempts by Mustafa were unsuccessful largely because reactions were conducted in dry ethereal solutions.<sup>327</sup>

The presence of ortho substituents on the C-phenyl ring of the imine also has an accelerating effect.<sup>182,331,341</sup> Based on spectral and kinetic evidence, it is suggested that the ortho substituent twists the phenyl ring out of the plane of the C=N bond, thus causing steric inhibition of resonance, which raises the ground-state energy and lowers the activation barrier of the imine.<sup>341</sup>

Alkylaluminum halides have been investigated as catalysts in the benzalaniline–diazomethane addition.<sup>342</sup> Reaction occurs at  $-78^{\circ}\text{C}$  in the presence of diethylaluminum chloride to yield the triazoline adduct; diethylaluminum iodide, however, leads only to an aziridine.

1,3-Dipolar cycloadditions are characterized by a negative volume of activation,<sup>343,344</sup> and diazomethane addition to benzalanilines is accordingly favored by an increase in pressure; at 5000 atm high yields of adducts are obtained.<sup>345</sup> Pressure facilitates the approach of diazomethane to the double bond of the imine.<sup>345</sup>

In the addition of diazoacetonitrile to para-substituted benzalanilines, unlike in the addition of diazomethane, electron-donating groups facilitate the



SCHEME 90

<sup>340</sup> F. Arndt, *Org. Synth., Collect. Vol.* **2**, 165 (1943).

<sup>341</sup> P. K. Kadaba, *J. Heterocycl. Chem.* **6**, 587 (1969).

<sup>342</sup> H. Hoberg, *Justus Liebigs Ann. Chem.* **707**, 147 (1967).

<sup>343</sup> R. A. Greiger and C. A. Eckert, *J. Am. Chem. Soc.* **92**, 2918, 7149 (1970); *Trans. Faraday Soc.* **66**, 2579 (1970).

<sup>344</sup> K. Seguchi, A. Sera, and K. Maruyama, *Tetrahedron Lett.*, 1585 (1973).

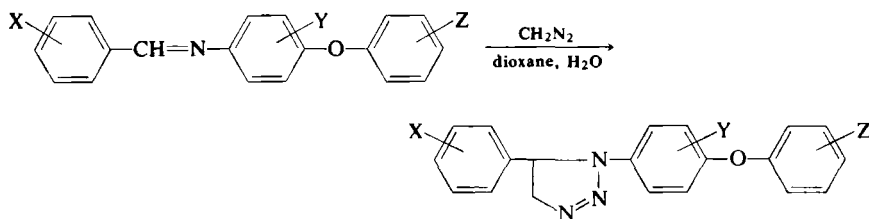
<sup>345</sup> H. de Suray, G. Leroy, and J. Weiler, *Tetrahedron Lett.*, 2209 (1974).

reaction, and two isomeric *cis*- and *trans*-triazolines have been isolated (Scheme 90).<sup>332</sup> In the absence of electron-donating groups, aziridines and/or enamines are obtained.<sup>332</sup> Similarly, the action of ethyl diazoacetate on benzalaniline leads directly to the enamine.<sup>284</sup>

The diazoacetonitrile-imine reaction may be considered complimentary to azide addition to cinnamionitriles because in the latter case only triazoline thermolysis products result.<sup>284</sup> The reversed order of reactivity of the diazoacetonitrile to that of diazomethane implies an electrophilic attack on the imine and is explained in terms of a  $\text{LUMO}_{\text{diazoacetonitrile}}-\text{HOMO}_{\text{imine}}$  controlled interaction. Thus electron-rich enamines, which do not react with diazoalkanes, may be expected to react with electron-poor diazo compounds.

## 2. Arylidenearyloxyanilines

Diazomethane addition to arylidenearyloxyanilines in dioxane-water<sup>330</sup> fails to give triazoline adducts in the majority of cases.<sup>346</sup> Where good yields of products are reported,<sup>346</sup> the reaction appears to be facilitated by the ortho substituents on the C-phenyl group<sup>331</sup>; the failure of the reaction in other cases appears to arise from the electron-releasing mesomeric effect of the 4-phenoxy substituent on the N-phenyl ring (Scheme 91).



SCHEME 91

## 3. Arylideneaminodiphenyl Sulfides and Sulfones

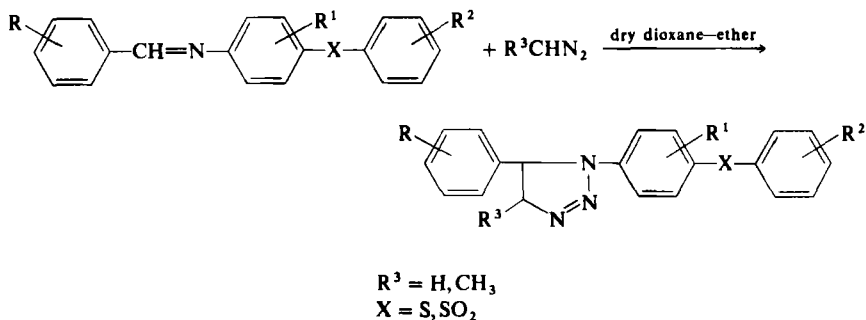
Both diazomethane and diazoethane add to these Schiff bases to give the 1,5- and 1,4,5-substituted triazolines, respectively (Scheme 92).<sup>347,348</sup> A nitro group in the para position on the diphenyl sulfone ring assists addition, but has no effect on the sulfide compounds. Also, few

<sup>346</sup> D. Dehne and M. Susse, *Z. Chem.* **16**, 102 (1976).

<sup>347</sup> M. A. Abbady, *Indian J. Chem., Sect. B* **16B**, 735 (1978) [*CA* **90**, 121498k (1979)].

<sup>348</sup> A. M. Osman and M. A. Abbady, *J. Prakt. Chem.* **320**, 1003 (1978).

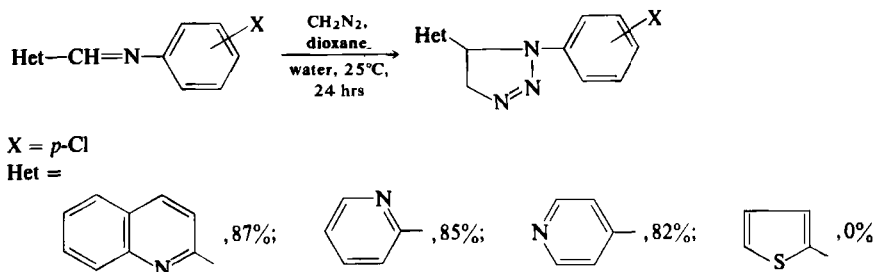
*o*-nitrobenzylideneaminodiphenyl sulfides are reported to undergo reaction.<sup>347,348</sup> Many of the inherently less reactive sulfides could have undergone addition if the reaction were not performed in dry dioxane–ether solution.<sup>182,330</sup>



SCHEME 92

#### 4. Heteroarylideneanilines

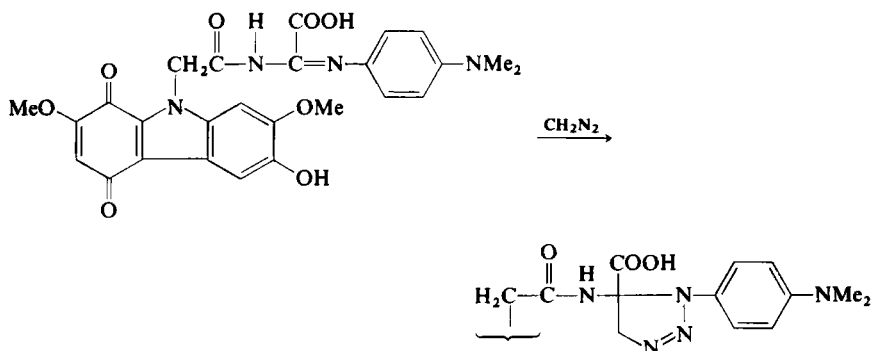
The cycloaddition of diazomethane to Schiff bases from heterocyclic aldehydes and anilines provides a useful route to heterocyclic substituted triazolines. Unlike olefins bearing heterocyclic substituents, the heterocyclic imines can be obtained readily by reaction of the appropriate aldehyde and amine; thus the diazomethane–imine addition has greater scope than the olefin–azide reaction. NMR spectroscopic studies of the orientation of addition are in accord with previously reported mechanistic considerations (see, e.g., Scheme 93).<sup>329</sup> In addition to the influence of the *N*-aryl group, the electron-withdrawing power of the heterocyclic substituent on the Schiff-base carbon also has a substantial effect on imine reactivity, in the order 2-quinolyl  $\approx$  2-, 3-, or 4-pyridyl  $>$  phenyl  $>$  2-thienyl  $\approx$  2-furyl.<sup>329</sup>



SCHEME 93

Schiff bases, derived from 2-(2,3-dihydropyran)carboxaldehyde and anilines, add diazomethane to give triazoline adducts in yields ranging from 45 to 66%.<sup>349</sup>

A triazoline adduct is also reported from the Schiff base formed from a peptide-bearing carbazoloquinone and diazomethane (Scheme 94).<sup>350</sup>



SCHEME 94

Reaction of diazomethane with 2-furylidene-4-aminodiphenyl sulfones<sup>347</sup> and 2-furylidene-4-carbethoxyanilines<sup>351</sup> yields the respective 5-(2-furyl)-substituted triazolines, which in some cases have been reported to have bactericidal activity at concentrations of  $10^{-1}$ – $10^{-5}$  M.<sup>347</sup>

Similarly, triazolines from anils and mixed azines of thiophenecarboxaldehyde and/or isatin also possess antimicrobial activity.<sup>352</sup>

### 5. Imines Derived from Heterocyclic Amines

Nitrobenzylidene-2-aminothiazoles undergo addition to diazomethane to yield 1-(2-thiazolyl)triazolines in moderate yields; the 2-hydroxybenzylidene compound fails to react (Scheme 95).<sup>353</sup> The prolonged reaction period could be shortened and the yields highly improved if dioxane–water were used as the reaction medium.<sup>182,329</sup>

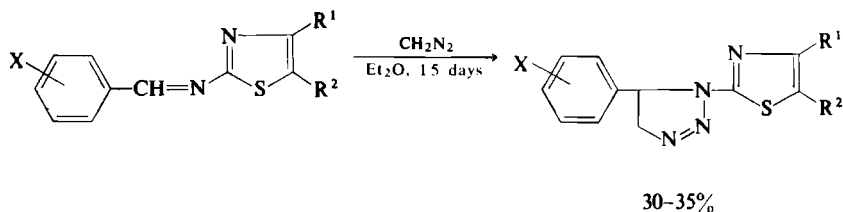
<sup>349</sup> I. A. Aleksandrova, A. V. Chernova, and V. K. Khairullin, *Khim. Geterotsikl. Soedin.*, 604 (1979).

<sup>350</sup> A. Hammam, *Indian J. Chem., Sect. B* 21B, 348 (1982).

<sup>351</sup> J. M. Stewart, R. L. Clark, and P. E. Pike, *J. Chem. Eng. Data* 16, 98 (1971).

<sup>352</sup> M. S. K. Youssef, *Rev. Roum. Chim.* 26, 471 (1981); *J. Chem. Technol. Biotechnol.* 31, 363 (1981).

<sup>353</sup> K. M. Hassan, M. A. El-Maghraby, H. S. El-Kashef, and A. K. El-Shafei, *J. Indian Chem. Soc.* 53, 903 (1976).



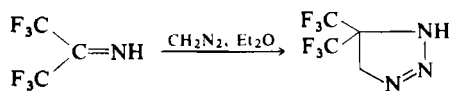
SCHEME 95

### 6. Heteroarylidene Heterocyclic Amines

Few additions have been attempted using imines prepared from heterocyclic aldehydes and heterocyclic amines. In the one example reported 1-(3-pyridyl)-5-(2-quinolyl)-1,2,3-triazoline is obtained in 70% yield after 21 hr.<sup>329</sup>

### 7. Aliphatic Imines

a. *Hexafluoroacetone Imine.* Although alkylidene alkylamines, in the absence of electron-withdrawing groups, are too sluggish to react with diazomethane, polyfluoroazaolefins show enhanced reactivity. Dipolar addition to fluoroolefins has received little attention and there are even fewer examples of addition to fluoroimines. Diazomethane addition to hexafluoroacetone imine is reported to be complete in 2 hr at 0°C, giving a 92% yield of the triazoline adduct with a free NH group (Scheme 96).<sup>354</sup>

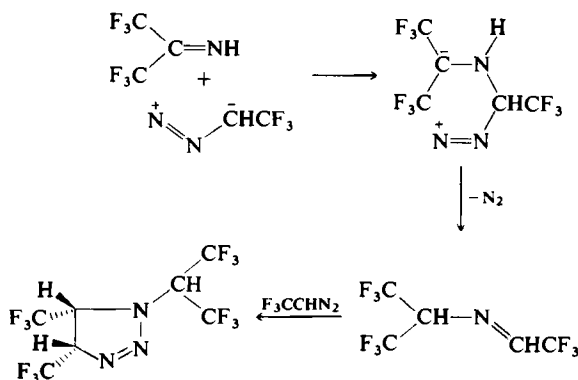


SCHEME 96

With trifluorodiazomethane, hexafluoroacetone imine undergoes initial N-alkylation followed by loss of nitrogen and formation of a new imine; the latter then undergoes cycloaddition with trifluorodiazomethane to give 55% of the triazoline along with 19% of the unchanged imine (Scheme 97). The fact that *N*-methylhexafluoroacetone imine fails to react with trifluorodiazomethane is taken as evidence for the initial N-alkylation step.<sup>355</sup>

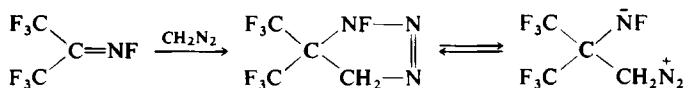
<sup>354</sup> I. L. Knunyants and Yu. V. Zeifman, *Izv. Akad Nauk SSSR, Ser. Khim.*, 711 (1967).

<sup>355</sup> R. Fields and J. P. Tomlinson, *J. Fluorine Chem.* 13, 19 (1979).



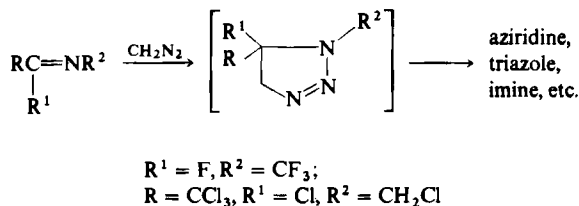
SCHEME 97

b. *N-Fluoroimines*. *N*-Fluoroimines of perfluoro ketones react readily with diazomethane at  $-50^\circ\text{C}$ ; moderate yields of unstable 1-fluorotriazolines, which exist in equilibrium with the open-chain dipolar tautomers, are obtained. Unlike normal triazolines, the inability of the 1-fluorotriazolines to undergo thermolysis or photolysis to yield aziridines is ascribed to the existence of this equilibrium, and conversion may be realized only by treatment with concentrated sulfuric acid (Scheme 98).<sup>356</sup>



SCHEME 98

c. *C-Fluoro- or Chloroimines*. *C*-Haloimines (imidoyl halides) bearing a halomethyl group on the nitrogen atom react readily with diazomethane to give unstable triazoline adducts that lose nitrogen or expel a molecule of



SCHEME 99

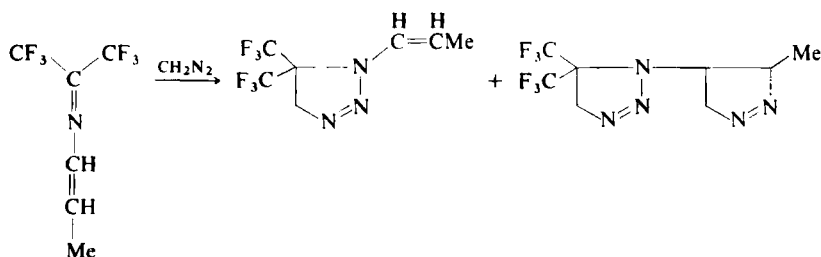
<sup>356</sup> B. L. Dyatkin, K. N. Makarov, and I. L. Knunyants, *Tetrahedron* **27**, 51 (1971).



hydrogen halide to yield the respective aziridine or triazole (Section IV) (Scheme 99).<sup>357,357a</sup> Similar reactions also take place with nonafluoroazacyclohex-1-ene.<sup>357</sup>

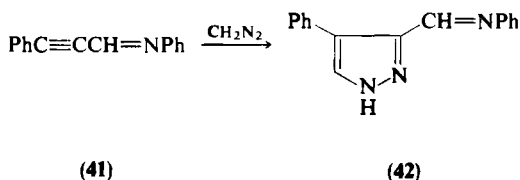
## 8. Azabutadienes

1,1-Bis(trifluoromethyl)-2-aza-1,3-butadiene reacts with diazomethane to give the 1-vinyltriazoline (1:1 adduct) or the *N*-pyrazolinyltriazoline (1:2 adduct), depending on the nature of the substituents in the 4-position of the azadiene (Scheme 100).<sup>358,359</sup> Diazomethane addition occurs preferentially to the more polar C=N bond and provides a route for the preparation of 1-vinyltriazolines; the reaction is complimentary to azide addition to conjugated dienes whereby 5-vinyltriazolines can be prepared.<sup>40</sup>



SCHEME 100

The analogous ethynyl imine (41), however, adds diazomethane to the acetylenic bond in preference to the imine bond; the latter presumably activates the acetylenic bond through its electron-withdrawing effect and appears at the 3-position of the pyrazole adduct (42).<sup>359a</sup>



<sup>357</sup> P. L. Coe and A. G. Holton, *J. Fluorine Chem.* **10**, 553 (1977).

<sup>357a</sup> H. Boehme and H. J. Drechsler, *Chem. Ztg.* **103**, 188 (1979).

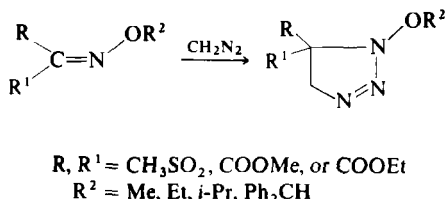
<sup>358</sup> K. Burger, J. Fehn, and A. Gieren, *Justus Liebigs Ann. Chem.* **757**, 9 (1972).

<sup>359</sup> A. Gieren, *Chem. Ber.* **106**, 288 (1973).

<sup>359a</sup> Yu. V. Shubina, D. A. Tikhomirov, and A. V. Ereemeev, *Khim. Geterotsikl. Soedin.*, 656 (1982).

## 9. Carbon–Nitrogen Double Bond in Oximes

*O*-Alkyl oximes substituted with electron-withdrawing groups on the carbon add diazomethane to give almost quantitative yields of the triazoline with the electron-withdrawing groups at the 5-position (Scheme 101)<sup>360</sup>; in azide addition to olefins, the electron-withdrawing groups appear at the 4-position of the triazoline molecule.<sup>67</sup>



SCHEME 101

The *O*-alkyl oximes of dialkyl mesoxalates have also been investigated<sup>361,362</sup>; the triazoline adducts undergo rapid decomposition at 20°C, at which reaction was performed, and give the required aziridines in 60–80% yields. Because of the presence of an ether substituent on the nitrogen, the oximes require two weeks for completion of reaction. *O*-Methyl ethers of acetoxime and biacetyl oxime do not react at all with diazomethane even after 3 months in ether at 20°C.<sup>361</sup>

When electron-withdrawing groups are present on both the carbon and nitrogen atoms of the oxime, triazoline adducts ranging in yield from 23 to 89% are obtained by reaction with diazomethane or diazoethane (Scheme 102); the aziridines formed from these triazolines are found to show unusual configurational stability.<sup>363,364</sup>

The reaction of the *O*-tosyloxime of dimethyl mesoxalate with diazomethane at 0 to –5°C in methylene chloride–ether for 1 hr gives a quantitative yield of the triazoline<sup>361</sup>; however, at 20°C the triazoline cannot

<sup>360</sup> H. J. Backer, *Recl. Trav. Chim. Pays-Bas* **69**, 1223 (1950).

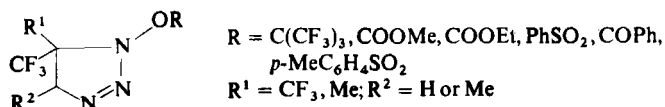
<sup>361</sup> R. G. Kostyanovskii, V. I. Markov, A. I. Mishchenko, and A. V. Prosyaniuk, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 250 (1977); A. I. Mishchenko, A. V. Prosyaniuk, A. P. Pleshkova, M. D. Isobaev, M. I. Markov, and R. G. Kostyanovskii, *ibid.*, 131 (1979); R. G. Kostyanovskii, A. V. Prosyaniuk, A. I. Mishchenko, G. V. Shustov, I. I. Chervin, N. L. Zaichenko, and V. I. Markov, *ibid.*, 1780.

<sup>362</sup> R. G. Kostyanovskii and V. F. Rudchenko, *Dokl. Akad. Nauk SSSR* **231**, 878 (1976); R. G. Kostyanovskii, V. F. Rudchenko, A. V. Prosyaniuk, M. D. Isobaev, I. I. Chervin, and V. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 628 (1977).

<sup>363</sup> R. G. Kostyanovskii and G. K. Kadorkina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1676 (1972).

<sup>364</sup> R. G. Kostyanovskii, G. K. Kadorkina, G. V. Shustov, and K. S. Zakharov, *Dokl. Akad. Nauk SSSR* **221**, 370 (1975).

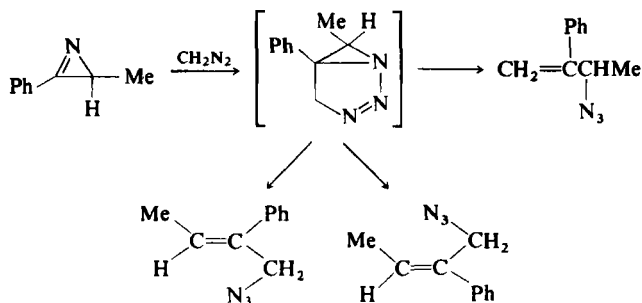
be isolated because it undergoes thermolysis. *O*-Tosylacetoxime does not react with diazomethane even after prolonged reaction.<sup>361</sup>



SCHEME 102

## 10. Azirines

The possibility of cycloaddition of diazomethane to the imine bond in azirines has been investigated<sup>365,366,366a</sup>; the products comprise a mixture of isomeric allyl azides, and it is possible that bicyclic triazolines are intermediates in this reaction (Scheme 103).<sup>366</sup>



SCHEME 103

## 11. Ketenimines and Carbodiimides

Diazoalkane adds to carbodiimides and ketenimines, preferentially to the carbon–nitrogen double bond of the latter, but the triazoline undergoes spontaneous isomerization to the triazole.<sup>367–371</sup> The only exception is the addition of ethyl diazoacetate to benzoyl isocyanate where an isolable

<sup>365</sup> A. L. Logothetis, *J. Org. Chem.* **29**, 3049 (1964).

<sup>366</sup> V. Nair, *J. Org. Chem.* **33**, 2121 (1968).

<sup>366a</sup> T. C. Gallagher and R. C. Storr, *Tetrahedron Lett.* **22**, 2909 (1981).

<sup>367</sup> M. W. Barker and J. H. Gardner, *J. Heterocycl. Chem.* **6**, 251 (1969).

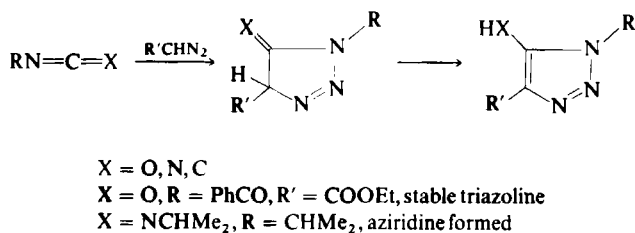
<sup>368</sup> M. F. Lappert and J. S. Poland, *J. Chem. Soc. C*, 3910 (1971).

<sup>369</sup> A. Martvon, S. Stankovsky, and J. Svetlik, *Collect. Czech. Chem. Commun.* **40**, 1199 (1975); J. Svetlik, J. Lesko, and A. Martvon, *Monatsh. Chem.* **111**, 635 (1980).

<sup>370</sup> R. Neidlen, *Chem. Ber.* **97**, 3476 (1964).

<sup>371</sup> H. Wieland, *Chem. Ber.* **40**, 1667 (1907); R. Rotter, *Monatsh. Chem.* **47**, 353 (1926); **51**, 245 (1931).

triazoline has been obtained (Scheme 104).<sup>370</sup> On the contrary, X-ray diffraction analysis indicates that the triazoline, formed from an isopropyl-substituted carbodiimide, decomposes to an aziridine, which then rearranges to an oxazoline (Scheme 104).<sup>372</sup>



SCHEME 104

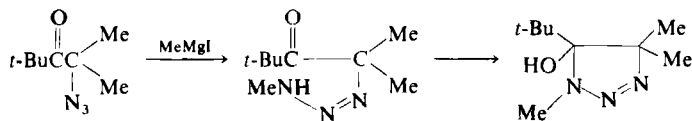
Site selectivity in ketenimine cycloadditions has been studied using photoelectron helium (HeI) spectra.<sup>372a</sup>

### C. OTHER ROUTES TO TRIAZOLINE SYNTHESIS

Although the olefin-azide and the imine-diazoalkane reactions constitute the two major general routes to triazoline synthesis, there are several other interesting pathways that have not been explored sufficiently and hence have only limited application.

#### 1. Cyclization of Triazenes

Based on the postulate that 5-hydroxytriazolines can exist in equilibrium with the open-chain triazene compounds in solution (Scheme 66),<sup>259,261-264</sup> one can envisage the cyclization of an appropriately substituted triazene to a triazoline. Thus the cyclization of a ketotriazene to a 5-hydroxytriazoline has been demonstrated (Scheme 105).<sup>258</sup>

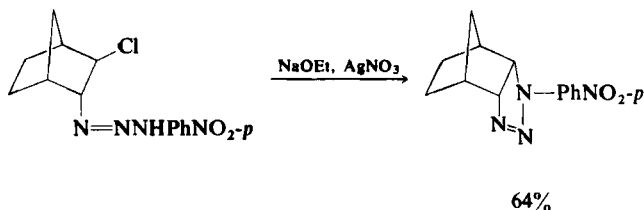


SCHEME 105

<sup>372</sup> J. Drapier, A. Feron, R. Warin, A. J. Hubert, and P. Teyssie, *Tetrahedron Lett.*, 559 (1979).

<sup>372a</sup> F. Bernardi, A. Bottoni, A. Battaglia, G. Distefano, and A. Dondoni, *Z. Naturforsch.*, A **35A**, 521 (1980).

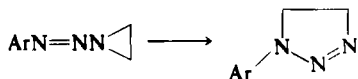
A second example is the formation of an *endo*-triazoline from a chloronorbornyltriazene compound, apparently by an intramolecular nucleophilic displacement reaction (Scheme 106).<sup>373</sup> Direct azide addition to norbornene is known to lead exclusively to the *exo* adducts (Section II,A,1).



SCHEME 106

## 2. From Arylazoaziridines

1-Arylazoaziridines rearrange to triazolines in an iodide- and thiocyanate-catalyzed reaction (Scheme 107)<sup>374</sup>; although this is one of the few procedures available for the preparation of 1-monosubstituted triazolines, the starting material is highly explosive and hazardous to handle.



SCHEME 107

## 3. Azide Addition to Sulfur Ylides

The addition of alkyl or aryl azides to dimethylsulfoxonium methylide provides a safer alternative route to the synthesis of N-monosubstituted triazolines (Scheme 108).<sup>375-377</sup> However, the generality of the method is limited because *p*-nitrophenyl and benzoyl azides yield only the vinyltriazenes (43); in order for triazoline cyclization to occur, the azide nitrogen bearing the substituent group should be sufficiently nucleophilic (see Scheme 108).

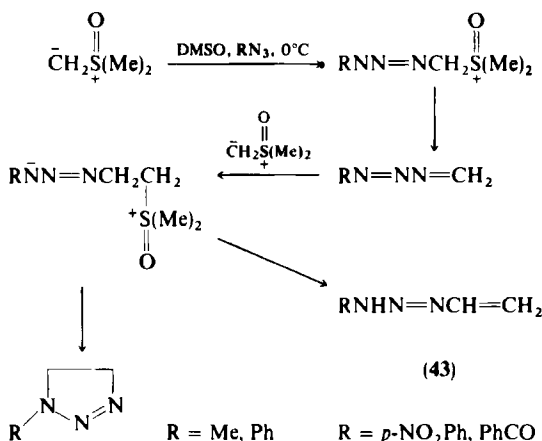
<sup>373</sup> L. H. Zalkow and R. H. Hill, *Tetrahedron Lett.*, 2819 (1972).

<sup>374</sup> H. W. Heine and D. A. Tomalia, *J. Am. Chem. Soc.* **84**, 993 (1962).

<sup>375</sup> G. Gaudiano, *Corsi Semin. Chim.* **10**, 12 (1968).

<sup>376</sup> G. Gaudiano, C. Ticozzi, A. Umani-Ronchi, and P. Bravo, *Gazz. Chim. Ital.* **97**, 1411 (1967).

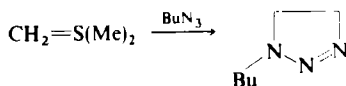
<sup>377</sup> G. Gaudiano, A. Umani-Ronchi, P. Bravo, and M. Acampara, *Tetrahedron Lett.*, 107 (1967).



SCHEME 108

Vinyl azides follow the same course of reaction when treated with dimethylsulfoxonium ylide in dimethyl sulfoxide at room temperature for 12 hr and high yields of clean 1-vinyltriazolines are obtained.<sup>378</sup>

The reaction of butyl azide with methylene dimethylsulfurane also leads to a triazoline (Scheme 109).<sup>379</sup>



SCHEME 109

Extensive studies on azide addition to keto-stabilized sulfur ylides have been conducted<sup>304,380-383</sup>; in addition to triazolines, various other products are also formed (Scheme 110). The betaine intermediate (44), resulting from the reaction of the azide with two molecules of the ylide, reacts in one of three ways, as determined by the nature of the R and R<sup>1</sup> substituents.

When the azide is strongly electron withdrawing (R = formate, benzoyl,<sup>304</sup> or substituted vinyl<sup>381</sup>), the betaine (44) does not cyclize to a triazoline; it gives the triazene (45) or adds another molecule of the ylide to give 47. In solution,

<sup>378</sup> A. Hassner, B. A. Belinka, Jr., M. Haber, and P. Munger, *Tetrahedron Lett.*, **22**, 1863 (1981).

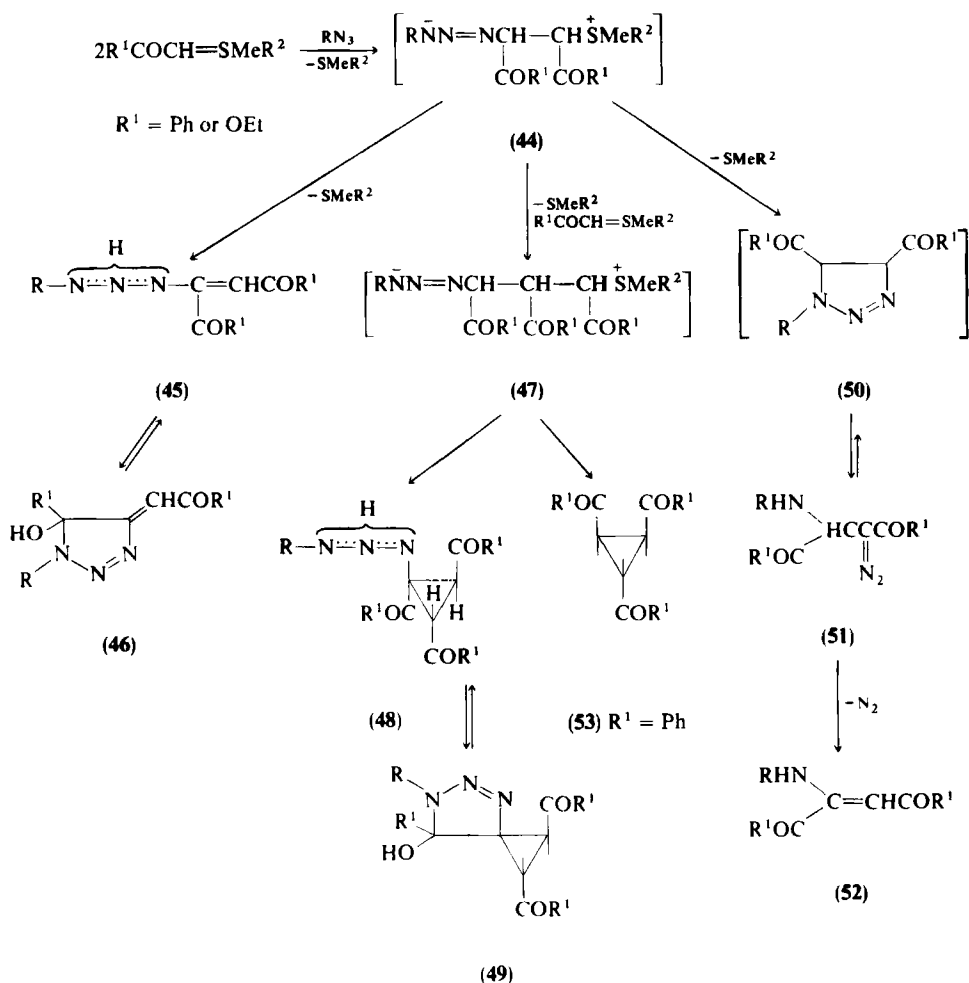
<sup>379</sup> See ref. 78 in ref. 2.

<sup>380</sup> G. L'abbé, *Angew. Chem., Int. Ed. Engl.* **14**, 775 (1975).

<sup>381</sup> G. L'abbé, G. Mathys, and S. Toppet, *Chem. Ind. (London)*, 278 (1975).

<sup>382</sup> E. Van Loock, G. L'abbé, and G. Smets, *Tetrahedron Lett.*, 1693 (1970).

<sup>383</sup> E. Van Loock, G. L'abbé, and G. Smets, *Tetrahedron* **28**, 3061 (1972).



SCHEME 110

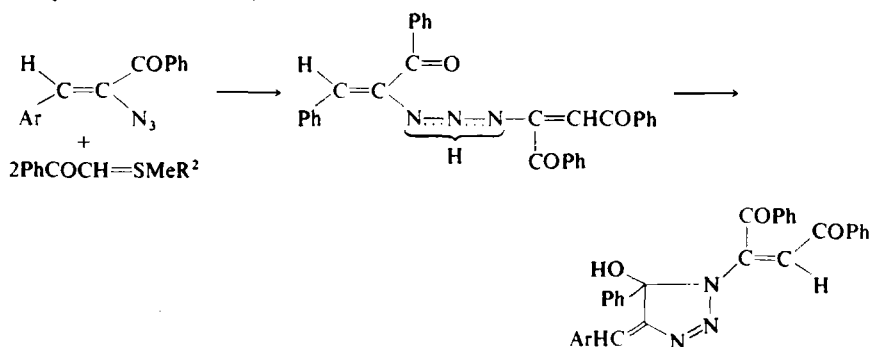
the triazene (45) exists in equilibrium with the 5-hydroxytriazoline (46). With ethyl azidoformate two conformational isomers differing in the spatial arrangement of the ester function have been obtained.<sup>381</sup>

The betaine (47) yields the triazene (48), which exists in equilibrium with the spirocyclopropanetriazoline (49) in chloroform solution.<sup>383</sup>

Reaction of the ylide with aryl azides leads to enamines (52) as the major product via the diazo ester (51) formed by the spontaneous isomerization of

the triazoline (**50**).<sup>304,384</sup> The triazene (**45**) as well as the cyclopropane (**53**) are also detected in the reaction medium. The reaction course is also strongly influenced by solvents; when  $R^1 = \text{OEt}$  and  $R = p\text{-NO}_2\text{Ph}$ , the triazene (**45**) formation predominates in benzene, whereas it is less than 10% in DMF.<sup>304</sup>

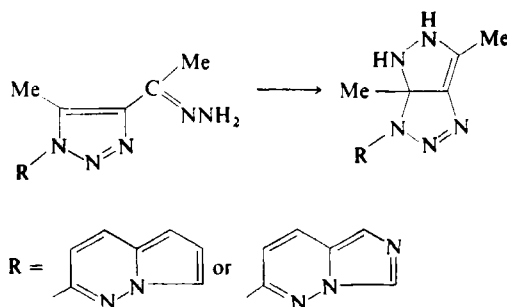
In the case of a vinyl azide substituted with a keto group, triazene cyclization occurs with the carbonyl group of the azide and not with that of the ylide (Scheme 111).<sup>381</sup>



SCHEME 111

#### 4. Isomerization of Triazole Hydrazones

Thermal isomerization of triazole hydrazones bearing a heterocyclic substituent on the ring nitrogen to a bicyclic triazoline has been observed, although limited to just two examples (Scheme 112).<sup>385</sup>



SCHEME 112

<sup>384</sup> Y. Hayashi, T. Watanabe, and R. Oda, *Tetrahedron Lett.*, 605 (1970).

<sup>385</sup> A. Gorup, M. Kovačič, B. K. Škraba, B. Mihelčič, S. Simonič, B. Stanovnik, and M. Tišler, *Tetrahedron* **30**, 2251 (1974).



### III. Structure and Physical Properties

#### A. STRUCTURE

Vicinal triazolines exist mainly in the 1*H* form. The parent compound is not known so far.

#### B. SPECTROSCOPIC PROPERTIES

##### 1. Ultraviolet Spectra

The majority of triazolines absorb in the region 390–310 nm ( $\epsilon = 6,000$ –10,000).<sup>24,113,346</sup> The UV spectra of triazolines display a marked sensitivity to the nature of the substituents at N-1; both the position and intensity of the absorption maximum are affected. On the other hand, the triazoline chromophore is not significantly influenced by substituents at positions 4 and 5 of the triazoline nucleus.<sup>79,113</sup>

The chromophoric properties of triazolines permit the application of UV spectroscopy for kinetic measurements of formation and decomposition of the triazoline adducts.<sup>24,79,113,205</sup> However, triazolines, when irradiated in the region of their UV absorption, undergo facile decomposition with nitrogen expulsion (Section IV,D,1).<sup>79,113</sup>

##### 2. Infrared Spectra

Triazolines show characteristic C=N absorption at approximately  $1620\text{ cm}^{-1}$ . In some instances, as in 1-phenoxyphenyl- $\Delta^2$ -1,2,3-triazolines, the C—O—C band appears at  $1250\text{ cm}^{-1}$ .<sup>346</sup> However, IR spectroscopy is mainly used to assign structures for triazoline decomposition products.<sup>197</sup>

##### 3. Mass Spectral Fragmentations

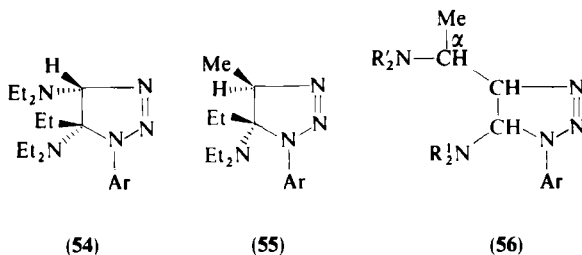
Most of the  $\Delta^2$ -triazolines undergo primary loss of a molecule of nitrogen in the mass spectrum and usually do not show a molecular ion peak. Initially, an  $M - 28$  peak is observed at higher temperatures ( $250^\circ\text{C}$ ) for triazolinonon-bornanes, but at lower temperatures ( $150^\circ\text{C}$ ), by increasing the sample pressure, an  $M + 1$  peak is obtained. The intensity ratio,  $M + 1/M - 28$ , is

found to vary with sample pressure, indicating a molecule-molecular ion interaction. No obvious stereochemical information is provided by the mass spectral studies.<sup>123</sup>

#### 4. Nuclear Magnetic Resonance Spectra

The N-1-substituted  $\Delta^2$ -1,2,3-triazolines exhibit two symmetrical multiplets of the type AA'BB' centered at approximately  $\delta$  4 ppm for the 4-CH<sub>2</sub> group and  $\delta$  3 ppm for the 5-CH<sub>2</sub> group.<sup>376</sup> The assignment of structures for adducts from unsymmetrical olefins and aryl azides is based on their NMR spectra. In several symmetrically substituted 4,5-dialkyltriazolines, the chemical shifts for the hydrogen at position 4, adjacent to the N=N linkage, are in the range of  $\delta$  4.1 to 4.7 ppm and for the hydrogen adjacent to the N-aryl group (H<sub>5</sub>), in the range of  $\delta$  3.6 to 4.0 ppm.<sup>40</sup>

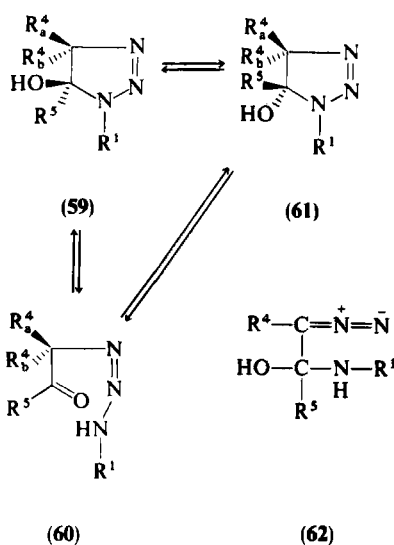
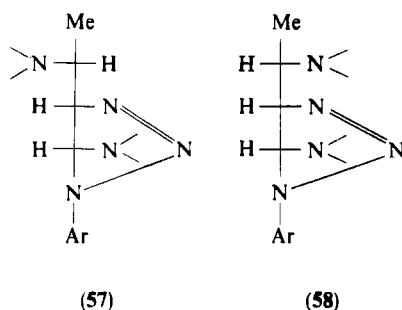
The NMR spectra of the diene adducts show complex multiplets in the region characteristic for H<sub>4</sub>,  $\delta$  4.1–4.7 ppm, whereas the signals for H<sub>5</sub> are displaced downfield to the H<sub>4</sub> region because of the presence of the adjacent vinyl group.<sup>40</sup> The cis and trans isomers of 1-aryl-5-dialkylamino- $\Delta^2$ -1,2,3-triazolines can be differentiated on the basis of their chemical shifts for H<sub>4</sub>, which appear at  $\delta$  4.21 and  $\delta$  4.54 ppm for the cis (**54**) and trans compounds (**55**), respectively.<sup>211</sup> NMR techniques are thus conveniently used to follow cis-trans isomerizations.<sup>211</sup>



Because 5-amino-4-( $\alpha$ -aminoethyl)-1-aryl- $\Delta^2$ -1,2,3-triazolines (**56**) show asymmetry at C-4, C-5, and C- $\alpha$ , four diastereoisomeric triazolines are theoretically possible. However, because the coupling constant  $J_{4,5}$  is never greater than 4 Hz, only two diastereomers need to be taken into consideration, the 4*SR*,5*RS*, $\alpha$ *RS* (**57**) and the 4*SR*,5*RS*, $\alpha$ *SR* (**58**). In isomer **57** the methyl doublet is always at lower field than the corresponding signal for isomer **58**. The H<sub>4</sub> signal is always at higher field for isomer **57** and the coupling constant  $J_{4,\alpha}$  is always greater for isomer **57** (8.5–9.9 Hz) than for isomer **58** (4.5–5.0 Hz), suggesting that in isomer **57** the population of high- $J$  rotamers is greater than

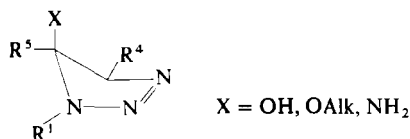
in isomer **58**. Based on this, and using molecular models, the  $4SR,5RS,\alpha RS$  configuration was assigned to triazoline **57** ( $J_{4,\alpha} = 8-9$  Hz) and the  $4SR,5RS,\alpha SR$  configuration to triazoline **58** ( $J_{4,\alpha} = 4.5-5.0$  Hz).<sup>227</sup>

Some of the 1-aryl-5-hydroxy- $\Delta^2$ -1,2,3-triazolines with two different substituent groups at C-4 exist in solution as a mixture of the diastereomers; they are readily interconvertible via a ketotriazene (**59–62**).<sup>259</sup> The compositions of the equilibrium mixtures for a number of 1-methyl- and 1-benzyl-5-hydroxy- $\Delta^2$ -1,2,3-triazolines in solution were determined by NMR spectroscopy. The  $\delta$  values of the methyl groups at C-4 fall into two regions, namely at  $\delta$  1.41–1.57 or 1.05–1.21. They can be oriented either *cis* or *trans* relative to the hydroxy group at C-5. The compounds with bulky substituents at C-5 exist only in one form in which the bulky C-5 group is *trans* to the methyl group at C-4. The



methyl group with a  $\delta$  value of about 1.48 ppm is cis to the hydroxy group at C-5; trans methyl groups give rise to signals at about 1.13 ppm.<sup>258</sup> Similar results were also obtained for 5-alkoxy- $\Delta^2$ -1,2,3-triazolines.<sup>26</sup> Chloroform-pyridine solvent shifts are larger for the cis ( $\sim -0.22$ ) than for the trans methyl groups ( $\sim -0.06$  to  $-0.15$  ppm). The assignments were confirmed by the  $\delta$  values for  $H_4$ , which fall into two ranges,  $\delta$  3.6–4.0 when  $H_4$  is trans to the hydroxy group and  $\delta$  4.1–4.5 when  $H_4$  is cis oriented.<sup>258</sup>

The chemical shifts for hydrogens and methyl groups at C-4 of 5-hydroxy- and 5-amino- $\Delta^2$ -1,2,3-triazolines depend on the orientation relative to the hetero substituent at C-5. This has been extensively used for assignment of relative configurations at C-4 and C-5 of variously substituted  $\Delta^2$ -triazolines.<sup>216,259</sup>  $^1\text{H}$ -NMR spectra show that 5-alkoxy- and 5-hydroxy- $\Delta^2$ -1,2,3-triazolines prefer an envelope conformation<sup>218</sup> (63) with the hetero substituent at C-5 pseudoaxial at the flap and the N-1 substituent pseudoequatorial, probably because of the anomeric effect. The cis and trans coupling constants in the 5-amino-, 5-hydroxy-, and 5-alkoxy- $\Delta^2$ -1,2,3-triazolines are very constant, being 7.0–9.8 and 2.0–3.4 Hz, respectively.<sup>218</sup>



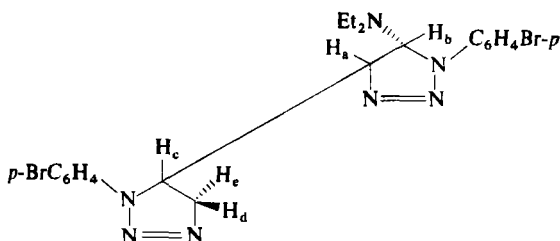
(63)

The chemical shifts for the hydrogen atoms at C-4 in 5-amino- $\Delta^2$ -1,2,3-triazolines, lying on the same side of the amino group at C-5, are always lower than those for hydrogen atoms on the opposite side. This can be applied to the determination of configuration because  $H_{4\text{-cis}}$  resonates at higher field ( $\delta$  4.07) than  $H_{4\text{-trans}}$  ( $\delta$  4.62). From the ABX system ( $H_5, H_{4\text{-cis}}$  and  $H_{4\text{-trans}}$ ) the coupling constants  $J_{\text{cis}} \cong 3$  and  $J_{\text{trans}} \cong 9$  Hz are calculated. This difference in the chemical shifts of the cis and trans hydrogen atoms is not affected by the nature of the aryl substituent.<sup>216</sup>

The structural assignments of the triazolines obtained by reaction of benzyl, methyl, and phenyl azides with olefins substituted by three electron-withdrawing substituents are based on  $^{13}\text{C}$ -NMR spectroscopy. The signal for C-4 appears in the region between 81 and 96 ppm and for C-5 in the region between 49 and 68 ppm with the coupling constants  $^1J_{\text{C-5/H}} = 146\text{--}161$  and  $^2J_{\text{C-4/C-5/H}} = 3.5\text{--}5.5$  Hz. When  $R = \text{CH}_3$  or  $\text{PhCH}_2$ , a coupling constant  $^3J_{\text{C/N/C-5/H}} = 3$  Hz is observed.<sup>282</sup>

The NMR spectrum of the bistriazoline (64) shows an ABX pattern ( $H_c, H_d, H_e$ ) partially overlapped with an AB pattern ( $H_a$  and  $H_b$ ) in the region

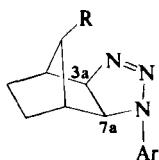
$\delta$  3.0–4.7, with the following coupling constants  $J_{ab} = 4$ ,  $J_{ac} = 3.7$ ,  $J_{cd} = 10.3$ ,  $J_{ce} = 7.5$ , and  $J_{de} = 17.8$  Hz. The low vicinal coupling constant  $J_{ac} = 3.7$  Hz suggests a threo configuration with the two molecules of azide attacking the double bond of the dienamine from opposite sides.<sup>238</sup>



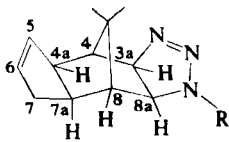
(64)

The reaction of 1-azidoadamantane with ethyl acrylate affords exclusively a 4-substituted triazoline.<sup>155</sup> The assigned regiochemistry is supported by  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra. The  $^1\text{H}$ -NMR spectral characteristics of the triazoline ring protons are similar to those reported for the corresponding adduct from phenyl azide.<sup>32</sup>  $^{13}\text{C}$ -NMR spectra reveal a characteristic triplet at  $\delta$  61.9 assignable to C-5.<sup>155</sup> Different NMR techniques have been used in structure assignments of isoindolo[2,1-*c*]- $\Delta^2$ -triazolines,<sup>324</sup> spiroanthrone-triazolines,<sup>193,194</sup> 5-heteroaryl-substituted  $\Delta^2$ -1,2,3-triazolines,<sup>329</sup> and some 1-fluoro-(5-trifluoromethyl)- $\Delta^2$ -1,2,3-triazolines.<sup>356</sup>

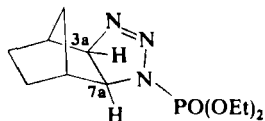
Exo–endo additions of organic azides to the norbornene skeleton and other bridged bicyclic systems can be easily differentiated from the NMR spectra of the adducts. The endo protons (exo adducts) of the norbornane do not couple with the bridgehead hydrogens.<sup>386</sup> The endo protons in position 3a and 7a of adduct **65** exhibit an AB spectrum. The lack of coupling with the bridgehead protons is a result of a dihedral angle of  $82^\circ$ .<sup>25,96</sup> Based on this, the exo form of cycloadduct **66** exhibits symmetrical doublets centered at  $\delta$  4.60 and



(65)

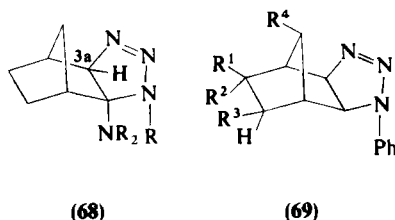


(66)

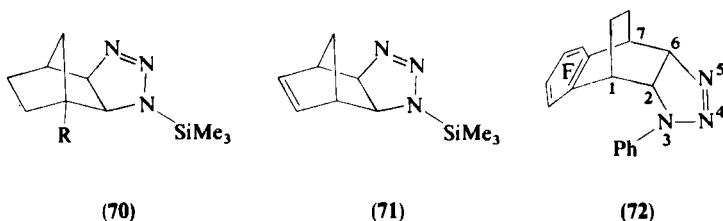


(67)

<sup>386</sup> F. A. L. Anet, *Can. J. Chem.* **39**, 789 (1961).

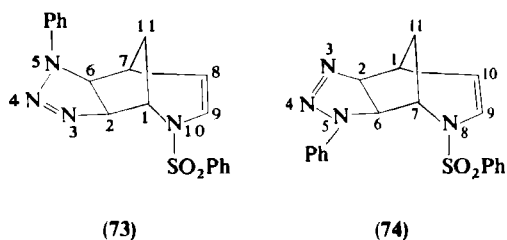


3.91 corresponding to H3a and H8a, respectively, with a coupling constant  $J_{3a,8a} = 8.8$  Hz.<sup>91</sup> Similarly, diethyl (3a,4,5,6,7,7a-hexahydro-4,7-methano-1*H*-benzotriazol-1-yl)phosphonate (67) shows an AB spectrum centered at  $\delta$  4.01 with  $J_{3a,7a} = 8.5$  Hz,<sup>105</sup> and adducts of the type 68 have a singlet for H3a at  $\delta$  3.65.<sup>213</sup> The NMR spectra of other exo adducts such as 69,<sup>124</sup> 65(R = OH),<sup>128</sup> 70, and 71,<sup>104</sup> have also been determined.



The endo adducts, on the other hand, show also the splittings with the bridgehead protons. For example, 3-phenyl-3,4,5-triazatetrafluorobenzo[8,9]tricyclo[5.2.2.0<sup>2,6</sup>-endo]undeca-4,8-diene (72) shows protons at  $\delta$  3.95 (H1), 4.16 (H2), 4.08 (H7), and 4.96 (H6) with the coupling constants  $J_{1,2} = 3.0$ ,  $J_{6,7} = 3.3$ , and  $J_{3,6} = 11.5$  Hz.<sup>169</sup> The fluorinated adducts have similar characteristics.<sup>89,161</sup>

The distinction between regioisomeric cycloadducts of nonsymmetrical, bridged bicyclic systems and organic azides has been achieved by observing the NMR chemical shifts, the coupling constants, and the nuclear Overhauser effect. For example, the exo regioisomers 73 and 74 show the following characteristics:



## CHEMICAL SHIFTS

Adduct	H <sub>1</sub>	H <sub>2</sub>	H <sub>6</sub>	H <sub>7</sub>	H <sub>8</sub>	H <sub>9</sub>	H <sub>10</sub>
<b>73</b>	~4.7	4.82	4.25	2.60	5.28	6.64	—
<b>74</b>	2.88	5.12	4.28	~4.4	—	6.66	5.49

## COUPLING CONSTANTS

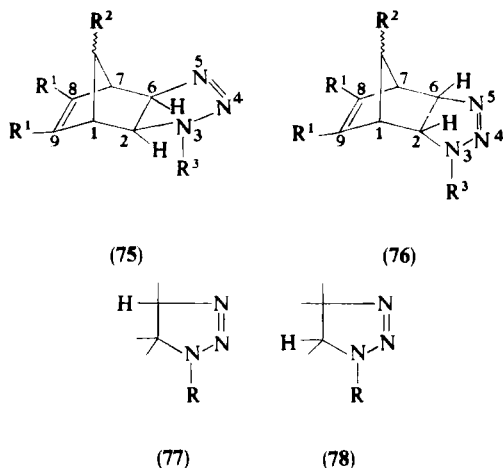
Adduct	$J_{1,2}$	$J_{2,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{9,10}$	$J_{10,1}$	$J_{7,9}$	$J_{1,9}$
<b>73</b>	0	9.5	0	7.5	7.5	—	—	0	1.0
<b>74</b>	0	9.5	0	—	—	7.5	7.5	1.0	0

Irradiation of the proton H7 of adduct **73** brought about an increase of 9% in the integral of the high field doublet for H6 and an increase of 9% in the integral of the vinyl proton H8 but no increase in the integral of the doublet for H2, thereby suggesting that the *N*-phenyl group and *N*-phenylsulfonyl group are on opposite sides of the molecule. Analogously, for adduct **74** irradiation of H1 shows that the *N*-phenyl group and the *N*-phenylsulfonyl group are on the same side of the molecule.<sup>92,132</sup> The shift reagent trisdipivalomethanoate europium(III) has been employed successfully for the structural assignments of nonsymmetrically substituted adducts of norbornenes and organic azides.<sup>123</sup>

The NMR spectral characteristics can also be used for the differentiation of syn- and anti-exo and syn- and anti-endo adducts. For example, substituted bicyclo[2.2.1]heptadienes form with phenyl azide adducts of type **75** and **76**, and in the syn-endo adducts **76** ( $R^1 = H$ ,  $R^2 = t\text{-OBu}$ ,  $R^3 = Ph$ ) the protons H2 and H6 appear at  $\delta$  4.51 and 5.48 ( $J_{2,6} \approx 10.0$  Hz). The deshielding effect is explained by the presence of the syn oxygen atom, whereas the measurable vicinal couplings with bridgehead protons H1 and H7 ( $J_{1,2} = 3.7$ ,  $J_{6,7} = 4.1$  Hz) are conclusive evidence for the endo configuration of the triazoline ring. For the anti-endo adduct of **76**, protons H2 and H6 appear at higher field ( $\delta$  4.20 and 5.15, respectively) coupled not only to each other but also to the bridgehead protons H1 and H7 ( $J_{1,2} = 3.7$ ,  $J_{6,7} = 4.1$ ,  $J_{2,6} = 10.0$  Hz). The syn-exo adduct **75** shows protons H1 and H6 at  $\delta$  4.12 and 4.85 ( $J_{2,6} = 10.0$  Hz), respectively, and the anti-exo adduct **75**, at  $\delta$  3.85 and 6.15 ( $J_{2,6} = 10.5$  Hz), with no measurable vicinal coupling constants  $J_{1,2}$  and  $J_{6,7}$ .<sup>99</sup>

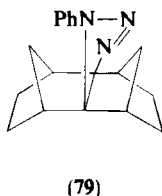
The structures of regioisomers, represented by the partial formulas **77** and **78** and formed by addition of organic azides to Bredt olefins, can be assigned unambiguously by <sup>1</sup>H- and <sup>13</sup>C-NMR spectra. In structure **77** the proton  $\alpha$  to the N=N double bond appears at lower field than the proton  $\alpha$  to the *N*-Ph group with approximately  $\Delta\delta = 0.8$  ppm. In the <sup>13</sup>C-NMR spectra a chemical

shift difference of more than 22 ppm is observed for the carbon atoms  $\alpha$  to single- or double-bonded nitrogen atoms.<sup>120</sup>



### C. X-RAY ANALYSIS

The crystal structures of 1-(4-methyl-1-pyrazolin-3-yl)-5,5-bis(trifluoromethyl)- $\Delta^2$ -1,2,3-triazoline, the 2:1 cycloadduct of diazomethane and 4-methyl-1,1-bis(trifluoromethyl)-2-aza-1,3-butadiene,<sup>359,387</sup> 1,4-dimethyl-5-hydroxy- $\Delta^2$ -1,2,3-triazoline (**63**,  $R^1 = R^4 = \text{CH}_3$ ;  $X = \text{OH}$ ),<sup>388</sup> and the *syn*-sesquinorbornene phenyl azide adduct (**79**)<sup>151</sup> have been solved by direct method.



For compound **63** the triazoline ring adopts an envelope conformation with C-5 at the flap of the envelope. The alkyl groups are equatorial, whereas the hydroxy group is axial. The interatomic distances and torsional angles are given in Tables II and III.<sup>388</sup>

<sup>387</sup> A. Gieren, K. Burger, and J. Fehn, *Angew. Chem.* **84**, 212 (1972); *Angew. Chem., Int. Ed. Engl.* **11**, 223 (1972).

<sup>388</sup> K. Kaas, *Acta Crystallogr., Sect. B* **29**, 1458 (1973).



TABLE II  
INTERATOMIC DISTANCES (Å) AND BOND ANGLES

Group	Interatomic distance (Å)	Group	Bond angles (degrees)
O—C-5	1.407 (2)	N-2—N-1—C-5	109.11 (14)
N-1—N-2	1.357 (2)	N-2—N-1—C-6	115.81 (17)
N-1—C-5	1.474 (3)	C-5—N-1—C-6	121.09 (19)
N-1—C-6	1.452 (4)	N-1—N-2—N-3	112.38 (16)
N-2—N-3	1.152 (2)	N-2—N-3—C-4	109.01 (17)
N-3—C-4	1.486 (3)	C-3—C-2—C-5	115.4 (2)
C-1—C-4	1.521 (3)	N-3—C-4—C-1	113.31 (17)
C-2—C-3	1.514 (4)	N-3—C-4—C-5	103.46 (15)
C-2—C-5	1.527 (3)	C-1—C-4—C-5	115.72 (19)
C-4—C-5	1.526 (3)	O—C-5—N-1	110.98 (15)
		O—C-5—C-2	105.96 (17)
		O—C-5—C-4	113.93 (16)
		N-1—C-5—C-2	112.64 (16)
		N-1—C-5—C-4	97.62 (15)
		C-2—C-5—C-4	115.76 (18)

TABLE III  
TORSIONAL ANGLES IN THE TRIAZOLINE RING

Atoms	Torsion angle (degrees)
N-1—N-2—N-3—C-4	0
N-2—N-3—C-4—C-5	17.9
N-3—C-4—C-5—N-1	-26.0
C-4—C-5—N-1—N-2	27.6
C-5—N-1—N-2—N-3	-19.1

#### D. OTHER PHYSICAL PROPERTIES

The dipole moment of 1-ethyl-1*H*-1,2,3-triazoline is experimentally determined to be  $\mu = 3.48$  D,<sup>389</sup> and the structure of 3-phenyl-3,4,5-triazatetrafluorobenzo[8,9]tricyclo[5.2.2.0<sup>2,6</sup>-endo]undeca-4,8-diene (**72**) has been confirmed by dipole measurements ( $\mu_{\text{exptl}} = 5.16$  D,  $\mu_{\text{calcd, endo}} = 4.91$  D,  $\mu_{\text{calcd, exo}} = 1.88$  D).<sup>169</sup>

Rates of phenyl azide addition have been correlated with ionization potentials for a number of strained olefins. The results show that about

<sup>389</sup> C. Pigenet and H. Lumbroso, *Bull. Soc. Chim. Fr.*, 3743 (1972).

20–25% of the ring-strain relief in the addition goes toward the lowering of the transition-state energy.<sup>170a</sup>

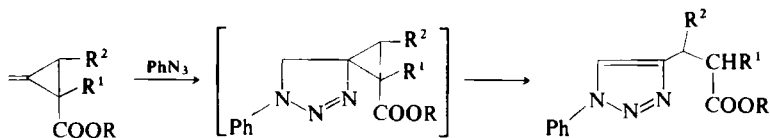
## IV. Reactions of 1,2,3-Triazolines

### A. AROMATIZATION TO TRIAZOLES

Triazoline aromatization to triazoles can be achieved by oxidation, isomerization reactions, and elimination of stable molecular fragments, all of which require the presence of a free hydrogen at position 4 and/or 5 of the triazoline ring. The aromatization reaction affords a selective, synthetic route for the preparation of triazoles of definitive structure, inasmuch as azide addition to acetylenes is not regioselective.<sup>33</sup>

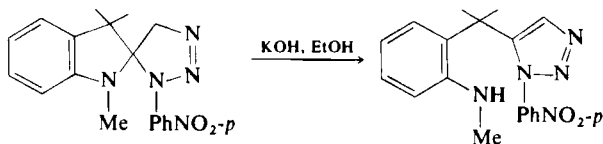
#### 1. Triazoline Isomerization

Spirocyclopropane<sup>173,390</sup> and spiroaziridine triazolines (Scheme 56)<sup>234</sup> undergo spontaneous isomerization to triazoles (Scheme 113).



SCHEME 113

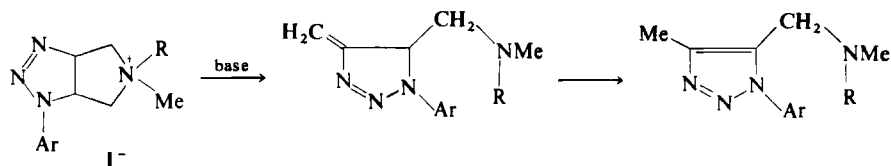
Isomerization can also be effected under the influence of a base (Scheme 114)<sup>233</sup>; the quaternary ammonium salt of an aminoalkyltriazoline isomerizes in an analogous manner (Scheme 115).<sup>179</sup> 5-Amino-1-aryl-4-methylenetriazolines also isomerize to 5-amino-1-aryl-4-methyltriazoles on reaction with nonnucleophilic bases.<sup>179,391</sup>



SCHEME 114

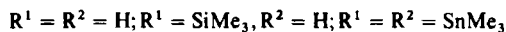
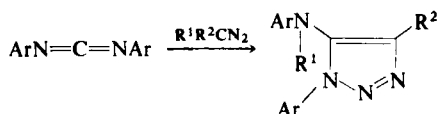
<sup>390</sup> J. C. Komin, *Diss. Abstr. Int. B* **35**, 1712 (1975).

<sup>391</sup> P. D. Croce, D. Pocar, R. Stradi, and P. Trimarco, *J.C.S. Perkin I*, 141 (1980).



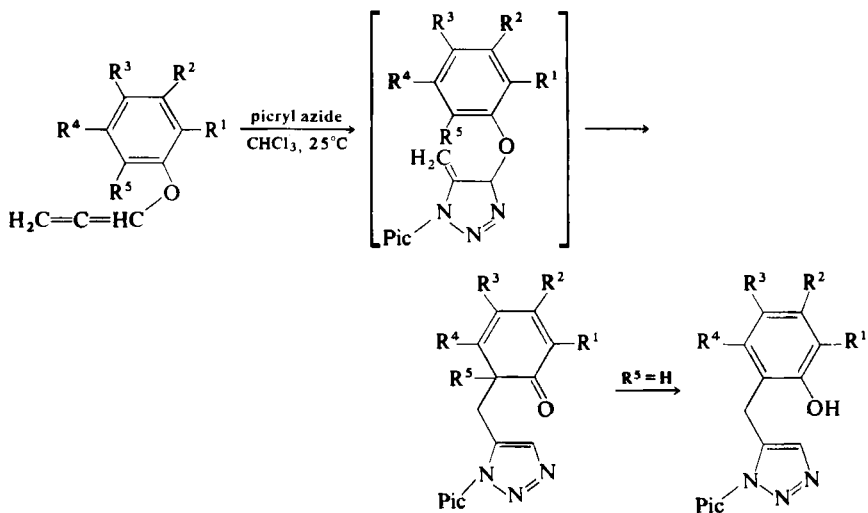
SCHEME 115

Triazolines resulting from the addition of diazoalkanes to ketenimines and carbodiimides generally isomerize spontaneously to triazoles (see Scheme 104).<sup>367-371</sup> Similarly, diazo compounds with carbodiimides also lead to triazoles (Scheme 116)<sup>368,369,371</sup>; the migratory aptitude of substituent groups  $R^1$  and  $R^2$  is of the order,  $\text{Me}_3\text{Sn} > \text{Me}_3\text{Si} > \text{H}$ .<sup>368</sup>



SCHEME 116

The intermediate methylenetriazolines from azide-allene reactions also give isomeric methyltriazoles.<sup>185,186,254,301</sup> The triazole formed in the

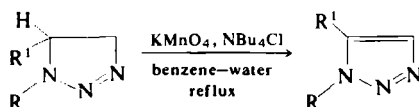


SCHEME 117

reaction of phenyl azide with aryloxyallenes apparently results from a Claisen rearrangement of the intermediate triazoline (Scheme 117)<sup>186</sup>; when  $R^5 = H$ , the triazole tautomerizes to the hydroxy compound.

## 2. Oxidation of Triazolines

In azide addition to quinones, the triazoline adducts are spontaneously oxidized to the triazoles.<sup>1,8,9,279-281,317,392,393</sup> Potassium permanganate<sup>32,155,286,288</sup> and nickel peroxide<sup>394</sup> also effect triazoline oxidation. Permanganate oxidation of 1,5-substituted triazolines in a two-phase system using a phase-transfer catalyst provides a convenient route to the synthesis of 1,5-disubstituted triazoles (Scheme 118).<sup>395,396</sup> Triazoline 4-carboxylic esters<sup>32,287,288</sup> and a 4-carboxamide<sup>397</sup> are converted to triazoles by potassium permanganate and nickel peroxide, respectively.



$R = \text{aryl}, R^1 = \text{aryl or heteroaryl}$

SCHEME 118

However, the possibility of equilibrium between triazoline 4-carboxylic esters and the ring-opened diazo compounds (Section II,A,4,a) poses a problem as to which entity is actually oxidized. In fact, the open-chain tautomers formed from the addition of phenyl azide to acrylic and cinnamic esters are oxidized in good yield to the triazoles by permanganate (Scheme 119).<sup>32,284,398</sup> When the diazo compound is formed with ease, the oxidation is very smooth<sup>284</sup>; thus the diazo compound from the addition of phenyl or methyl azide to benzylideneacetone is oxidized rapidly in air to a triazole-4-carboxylic ester.<sup>284</sup> A similar mechanism may be proposed to

<sup>392</sup> F. R. Benson and W. L. Savell, *Chem. Rev.* **46**, 1 (1950).

<sup>393</sup> E. Hoggarth, in "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. 4A, p. 439. Elsevier, Amsterdam, 1957.

<sup>394</sup> P. K. Kadaba and M. A. Bertrand, unpublished results.

<sup>395</sup> P. K. Kadaba, *Synthesis*, 694 (1978).

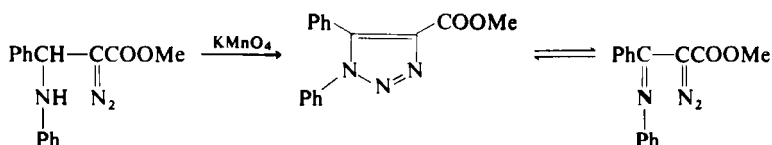
<sup>396</sup> P. K. Kadaba, *J. Prakt. Chem.* **324**, 857 (1982).

<sup>397</sup> D. L. Evans, D. K. Minster, U. Jordis, S. M. Hecht, A. L. Mazzu, Jr., and A. I. Meyers, *J. Org. Chem.* **44**, 497 (1979).

<sup>398</sup> Y. Tanaka and S. I. Miller, *J. Org. Chem.* **37**, 3370 (1972).

account for the unusual formation of 1,5-diphenyl-4-nitro- and 4-benzoyl-triazoles in the respective reactions of phenyl azide with  $\beta$ -nitrosytrene<sup>284,297</sup> and benzylideneacetophenone.<sup>309a</sup>

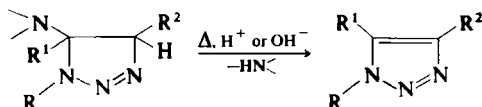
The oxidation of diazo compounds to triazoles may proceed via an iminodiazocompound in equilibrium with the triazole (Scheme 119)<sup>285,399</sup>; an iminodiazocompound is formed quantitatively in the reaction of tosyl azide with ethoxyethylene.<sup>400</sup>



SCHEME 119

### 3. Elimination of Stable Fragments

a. *Elimination of Amine.* 5-Aminotriazolines with a free hydrogen in the 4-position aromatize readily under the influence of heat by elimination of a molecule of amine (Scheme 120). The reaction occurs spontaneously in many cases, with a tertiary amino substituent, during azide-enamine addition, and the products isolated are triazoles<sup>35,38,39,210,215,239</sup>; amine elimination is facilitated further when  $\text{R}^2$  is an electron-withdrawing substituent (see also Section II,A,3,d, Scheme 61).<sup>214,246,248,249,401</sup>



R = alkyl or aryl

SCHEME 120

When  $\text{R}^1 = \text{CN}$ , a molecule of hydrogen cyanide is lost and the 5-amino-triazole is obtained.<sup>249</sup> Spontaneous amine elimination also occurs when  $\text{R}^2$  is hydrogen and an aliphatic secondary amino group is present,<sup>214</sup> which is similar to what is observed in the addition of tosyl azide to  $\beta$ -enamino esters<sup>233</sup> and nitriles.<sup>402</sup> Thermal elimination of amine proceeds more

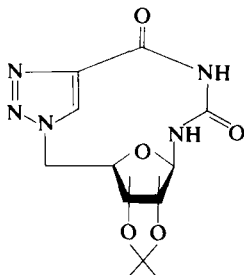
<sup>399</sup> M. Regitz and G. Himbert, *Tetrahedron Lett.*, 2823 (1970).

<sup>400</sup> P. Grunanger, P. Vita Finzi, and C. Scotti, *Chem. Ber.* **98**, 623 (1965).

<sup>401</sup> D. Pocar, S. Maiorana, and P. D. Croce, *Gazz. Chim. Ital.* **98**, 949 (1968).

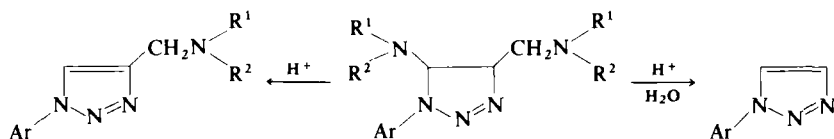
<sup>402</sup> K. Harsanyi, K. Takacs, E. Benedek, and A. Neszmelyi, *Liebigs Ann. Chem.*, 1606 (1973).

rapidly when the amino group is trans with respect to the C-4 hydrogen.<sup>403</sup> Although usually triazolines derived from cyclic enamines do not aromatize,<sup>39</sup> the triazoline shown in Scheme 57 aromatizes to a triazole (**80**) that remains in equilibrium with the triazoline.<sup>235</sup>



(80)

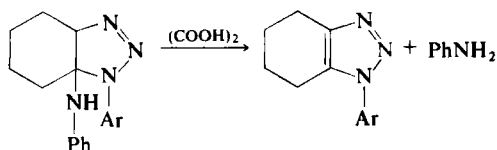
Amine elimination can also be effected under the action of an acid<sup>35,39,210,220,222,229,230,232</sup> or a base.<sup>31,37,209,227-229,238,391,403</sup> The action of acids on 5-aminotriazolines is not a general reaction; the products vary and are dependent on the substituents. Usually, the more stable triazolines yield the triazoles; alkyl groups in the 4- and 5-positions cause ring-cleavage reactions. In Scheme 120, when  $R^1$  is hydrogen and a tertiary amino group is present, acids cause ring breakdown; in another case, depending on the concentration of the acid, two different triazoles are obtained (Scheme 121).<sup>228</sup>



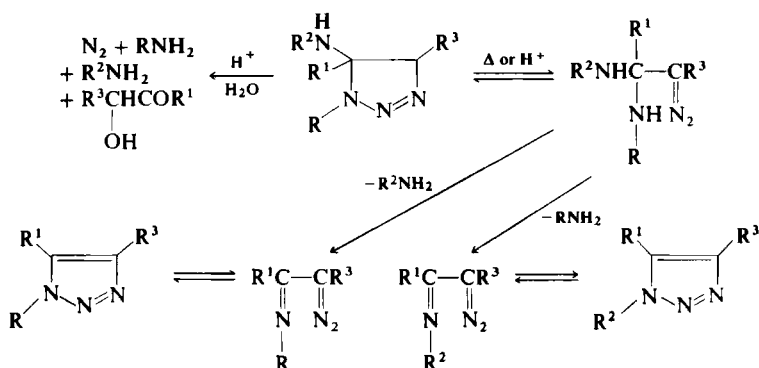
SCHEME 121

The bicyclic triazoline in Scheme 122 substituted with a secondary aryl-amino group gives a triazole,<sup>208</sup> but only degradation products are obtained from the triazoline in Scheme 123, bearing an aliphatic amino group, when treated with dilute acid.<sup>208</sup> However, in an anhydrous medium under the action of heat or *p*-toluenesulfonic acid, two possible modes of amine elimination can occur and two different triazoles are formed (Scheme 123).<sup>214,223,224</sup>

<sup>403</sup> See ref. 209 in ref. 2.



SCHEME 122



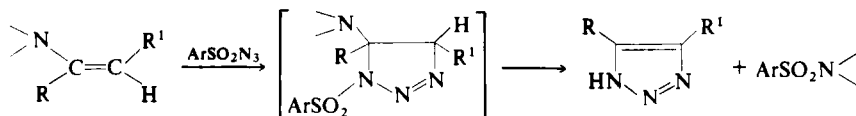
SCHEME 123

The intermediate diazo compound can eliminate either  $\text{R}^2\text{NH}_2$  or  $\text{RNH}_2$ ; when R is an aryl and  $\text{R}^2$  is an alkyl group, the less nucleophilic  $\text{RNH}_2$  is eliminated and forms the basis for the simple synthetic route to *N*-alkyltriazoles by aryl azide addition to enolizable imines in the presence of *p*-toluenesulfonic acid.<sup>224</sup> Enolizable imines that can exist in two tautomeric forms (see Scheme 53) lead to two isomeric *N*-alkyltriazoles.<sup>224</sup> With dilute acid, the intermediate triazolines undergo ring degradation.<sup>224</sup> When R is an alkyl group similar to  $\text{R}^2$ , both triazoles are obtained<sup>214</sup>; but when  $\text{R}^3$  is an electron-withdrawing substituent, direct elimination of  $\text{R}^2\text{NH}_2$  occurs regardless of whether R is alkyl or aryl.<sup>214</sup> Ring-degradation reactions with dilute acids are more common among the more basic aminotriazolines because they are more easily protonated.<sup>208,228</sup>

An interesting case of triazole formation under the influence of base is that of the bistriazoline in Scheme 58, which expels a molecule of diethylamine and yields two molecules of 1-*p*-bromophenyltriazole.<sup>238</sup> 1-Vinyl-5-aminotriazolines are readily deaminated to the corresponding triazoles when eluted through a silica-gel column.<sup>222</sup>

Although the addition of arylsulfonyl azides to enamines usually leads to amidines by loss of nitrogen from the intermediate triazoline adduct, when an electron-withdrawing substituent is present in the  $\beta$ -position of the

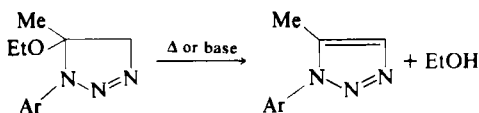
enamine, *N*-H-triazoles are formed by elimination of a sulfonamide (Scheme 124).<sup>247,248,401</sup> When  $R = \text{Me}$  and  $R^1 = \text{COPh}$  or  $\text{CONHPh}$ , thermolysis enters into competition with triazole formation.<sup>247</sup>



SCHEME 124

*N*-H-Triazoles are also formed by catalytic hydrogenation of certain 5-amino-1-alkoxycarbonyltriazolines in an acid medium, but the reaction is accompanied by a hydrogenolysis of the N-1-C bond.<sup>30</sup>

b. *Elimination of Alcohol and Water.* 5-Alkoxytriazolines, similar to the 5-amino compounds, lead to triazoles by eliminating a molecule of alcohol under the action of heat or a base (Scheme 125).<sup>26,39</sup> If the vinyl ether-azide addition (see Scheme 62) is conducted in the presence of a base, only the triazole is isolated.<sup>39</sup> Vinyl acetate and phenyl azide in an analogous reaction eliminate acetic acid to give the triazole.<sup>39</sup>



SCHEME 125

5,5-Dialkoxytriazolines with a free hydrogen at C-4 (Scheme 67)<sup>266,267,269,404</sup> and the corresponding open-chain diazo isomers (Scheme 68)<sup>272,273</sup> both lead to 5-alkoxy triazoles by heating or, as in the latter case, by the action of a base.<sup>405</sup>

The thermolysis of 1- $\beta$ -ethoxyethyl-5-alkoxytriazolines at  $170^\circ\text{C}$  proceeds in two directions (Scheme 126); although triazole formation predominates, loss of nitrogen becomes increasingly important as the length of the 5-alkoxy chain increases.<sup>406</sup>

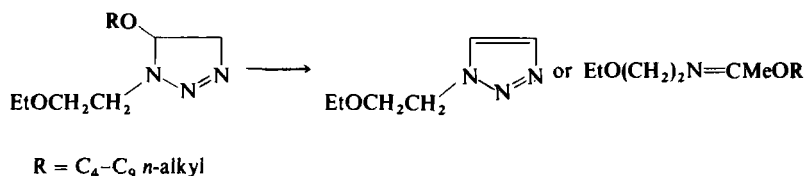
5-Hydroxytriazolines, isolable or formed in transit (Scheme 64)<sup>255,261,263</sup> undergo aromatization by dehydration. 1-Alkyl-5-hydroxytriazolines can be dehydrated by the action of trifluoroacetic acid<sup>256,262</sup>; however, the 1-aryl counterpart loses nitrogen to give various rearrangement products.<sup>262</sup>

<sup>404</sup> M. L. Graziano, R. Scarpati, and E. Fattorusso, *J. Heterocycl. Chem.* **11**, 529 (1974).

<sup>405</sup> R. Scarpati and M. L. Graziano, *Tetrahedron Lett.*, 2085 (1971).

<sup>406</sup> G. A. Lanovaya and V. F. Mishchenko, *Zh. Org. Khim.* **15**, 2203 (1979).

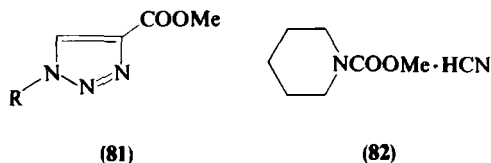




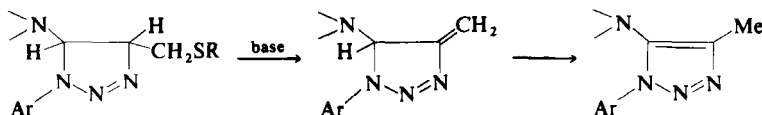
SCHEME 126

c. *Elimination of Nitrous, Hydrocyanic, and Other Acid Fragments.* Triazolines substituted on the carbons with one or two strong electron-withdrawing groups are seldom isolated because they aromatize spontaneously or under the influence of heat or a base to give triazoles by loss of stable acidic fragments (see Scheme 77, Section II,A,4 and Scheme 99, Section II,B,7,c).<sup>89,155,293–296,298,299,357,357a</sup> 4,5-Dicyano- and 4,5-dibenzoyltriazolines lose hydrogen cyanide and benzaldehyde to give the respective 4-cyano-<sup>32,306</sup> and 4-benzoyltriazoles.<sup>306</sup> When the electron-withdrawing groups are in a geminal position on the 4- (e.g., Br and COOR)<sup>291</sup> or 5-carbon (e.g., NO<sub>2</sub> and COR) (Scheme 84),<sup>323</sup> the more electronegative bromo and nitro groups are eliminated.

When three electron-withdrawing groups are present (Scheme 85, Y = COOMe and X = CN), treatment with piperidine results in elimination of the cyano as well as one of the 4-substituents, and the products are **81** and **82**.<sup>282</sup>



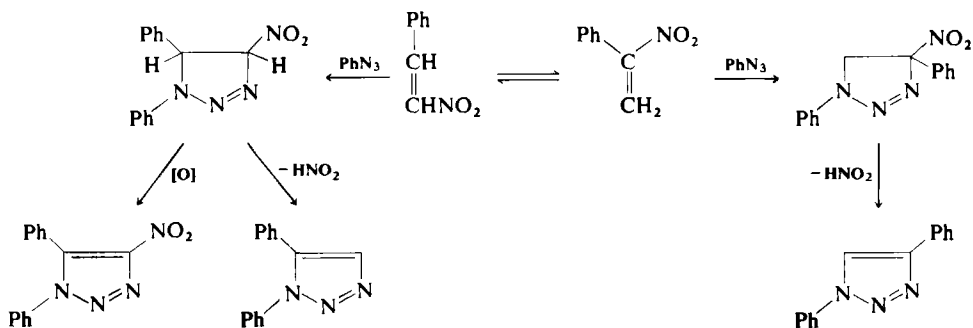
1-Aryl-4-alkyl(or aryl)thiomethyl-5-aminotriazolines undergo amine or thiol elimination with a base (Scheme 127).<sup>217</sup> The fused-ring 5-azido-triazoline (**32**, Scheme 41), under the influence of heat or a base, eliminates hydrazoic acid and yields the corresponding tetracyclic triazole.<sup>200</sup>



SCHEME 127

Reaction of 1-azidoadamantane with nitro and sulfoxyl olefins (Scheme 77,  $R' = H$  or  $Ph$  and  $X = NO_2$ ;  $R' = Ph$  and  $X = SPh$ ) leads directly to the triazoles; two isomers are obtained from the  $\beta$ -nitrostyrene reaction with the 5-phenyl-1-adamantyltriazole as the major product.<sup>155</sup> Likewise, triazoles are the only products formed in the reaction of aryl azides with  $\beta$ -nitrostyrene (Scheme 77)<sup>294,295</sup>; however, unlike the azidoadamantane reaction, a 1,5-diphenyl-4-nitrotriazole is also obtained.<sup>295</sup> Sodium azide also reacts with olefins in Scheme 77, leading to triazoles unsubstituted on the nitrogen.<sup>295,296,298,299,323</sup>

The isomeric triazoles do not arise from a lack of regioselectivity in azide addition to  $\beta$ -nitrostyrenes as shown in Scheme 77<sup>155,294,295</sup>; instead, an initial isomerization of the nitroolefin followed by regioselective azide addition to the olefinic isomers has been proposed (Scheme 128).<sup>284,297</sup> The 1,5-diphenyl-4-nitrotriazoline can undergo oxidation (Section IV,A,2)<sup>284</sup> to give the 4-nitrotriazole or expel a molecule of nitrous acid.



SCHEME 128

d. *Elimination of Phosphine Oxide.*  $\alpha$ -Acyl and  $\alpha$ -ethoxycarbon-ylphosphorus ylides undergo 1,3-dipolar cycloaddition with organic azides to give triazoline adducts from which phosphine oxide is spontaneously eliminated (Scheme 129).<sup>407-410</sup> The ylides, which exist almost exclusively in the cis-enolate configuration act as dipolarophiles, and the reactivity order of the azides,  $R = Ts > RCO > p\text{-NO}_2\text{Ph} > Ph > \text{alkyl}$ , corresponds to a  $LUMO_{\text{azide}}\text{-}HOMO_{\text{ylide}}$  orbital interaction.<sup>65</sup> Numerous triazoles have been synthesized by this reaction scheme in which  $R^1 = \text{alkyl, aryl, or ethoxy, and}$

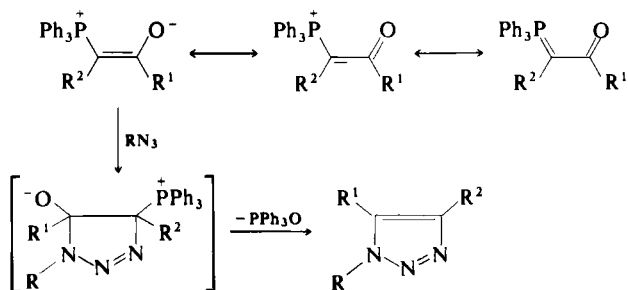
<sup>407</sup> G. L'abbé, P. Ykman, and G. Smets, *Bull. Soc. Chim. Belg.* **78**, 147 (1969).

<sup>408</sup> G. L'abbé, P. Ykman, and G. Smets, *Tetrahedron* **25**, 5421 (1969).

<sup>409</sup> P. Ykman, G. L'abbé, and G. Smets, *Tetrahedron* **27**, 845 (1971).

<sup>410</sup> P. Ykman, G. L'abbé, and G. Smets, *Tetrahedron* **27**, 5623 (1971).

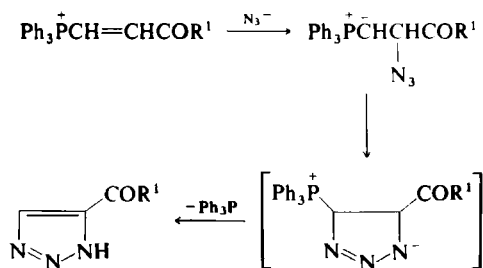
$R^2 = \text{H, alkyl, or alkenyl, using aryl,}^{409,411,412} \text{ acyl,}^{407,410-414} \text{ alkoxycarbonyl,}^{410,412,415} \text{ vinyl,}^{416} \text{ and tosyl}^{411} \text{ azides.}$



SCHEME 129

With acyl and alkoxycarbonyl azides, 2*H*-triazoles are formed by isomerization of the 1*H* compounds,<sup>410</sup> and changes in  $R^1$  and  $R^2$  substitution lead to diazo compounds and iminophosphoranes rather than triazoles,<sup>408,411,412,415</sup> owing to competitive addition to the  $\text{C}=\text{P}$  bond. Reaction of cyanogen azide with  $\alpha$ -acylphosphorus ylides leads to 1-cyanotriazoles, which undergo *in situ* ring opening to give *N*-cyano- $\alpha$ -diazoimines.<sup>417</sup>

Reaction of vinyl phosphonium salts with sodium azide also yields triazoles via triazolone intermediates by elimination of triphenylphosphine (Scheme 130).<sup>418</sup>



SCHEME 130

<sup>411</sup> G. R. Harvey, *J. Org. Chem.* **31**, 1587 (1966).

<sup>412</sup> P. Ykman, G. L'abbé, and G. Smets, *Tetrahedron* **29**, 195 (1973).

<sup>413</sup> P. Ykman, G. L'abbé, and G. Smets, *Tetrahedron Lett.*, 5225 (1970).

<sup>414</sup> E. Zbiral and J. Stroh, *Monatsh. Chem.* **100**, 1438 (1969).

<sup>415</sup> G. L'abbé and H. J. Bestmann, *Tetrahedron Lett.*, 63 (1969).

<sup>416</sup> P. Ykman, G. Mathys, G. L'abbé, and G. Smets, *J. Org. Chem.* **37**, 3213 (1972).

<sup>417</sup> B. Arnold and M. Regitz, *Tetrahedron Lett.* **21**, 909 (1980).

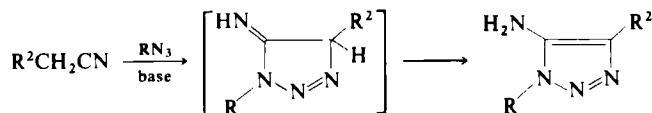
<sup>418</sup> M. Rasberger and E. Zbiral, *Monatsh. Chem.* **100**, 64 (1969).

#### 4. Aromatization of Triazolines Derived from Active Methylene Compounds

Azide addition to an active methylene compound in the presence of a base involves a triazoline intermediate that aromatizes to a triazole; the reaction is a well-established route to 1*H*-triazoles<sup>6,8</sup> bearing a 5-amino or hydroxy substituent and an aryl or carbonyl-containing function in the 4-position. The proposed triazoline intermediates have been detected in the reaction of azides with aliphatic ketones (see Scheme 64, Section II,A,3,f).

In most cases, although the activated methylene group is flanked on both sides by electron-withdrawing substituents and cyclization could take place in two different ways, in practice, cyclization almost invariably occurs only in one direction. When one of the activating groups is a nitrile, 5-aminotriazoles are formed (Scheme 131) and when it is a carbonyl, triazoles with or without a functional group are obtained (Scheme 132).<sup>8,419</sup> When  $R^1$  is ethoxyl, it appears as the hydroxyl in the triazole.  $\alpha$ -Cyanoacetophenone acts as a carbonyl-activated compound and gives 4-cyano-5-phenyltriazoles.<sup>420</sup> The reactions have been carried out using a variety of azides: alkyl,<sup>255,261</sup> aryl,<sup>8,255,261,421-424</sup> alkoxycarbonyl,<sup>425</sup> sulfonyl,<sup>402,425</sup> vinyl,<sup>420,426</sup> heterocyclic,<sup>385,427</sup> and azidotropolones.<sup>419</sup>

In the reaction of nitrile compounds with aryl azides bearing a carboxyl<sup>424</sup> or nitrile<sup>423</sup> function in the ortho position, fused triazoles are formed by further reaction of the 5-amino group with the ortho substituent on the 1-phenyl ring. Whereas  $\alpha$ -cyanomethylene phosphonate gives the expected



SCHEME 131

<sup>419</sup> H. Horino and T. Toda, *Bull. Chem. Soc. Jpn.* **46**, 1212 (1973).

<sup>420</sup> S. Maiorana, *Ann. Chim. (Rome)* **97**, 1531 (1967).

<sup>421</sup> A. Dornow and J. Helberg, *Chem. Ber.* **93**, 2001 (1960).

<sup>422</sup> U. Heep, *Liebigs Ann. Chem.*, 578 (1973).

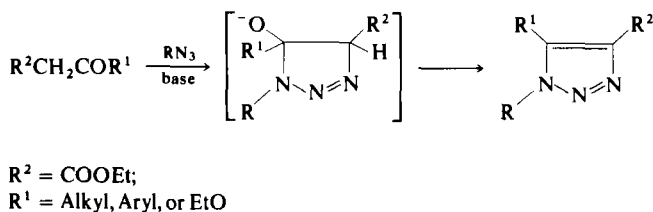
<sup>423</sup> D. R. Sutherland and G. Tennant, *J.C.S., Perkin I*, 534 (1974).

<sup>424</sup> G. Tennant, *J. Chem. Soc. C* 2290 (1966).

<sup>425</sup> R. Mertz, D. Van Assche, J. P. Fleury, and M. Regitz, *Bull. Soc. Chim. Fr.*, 3442 (1973).

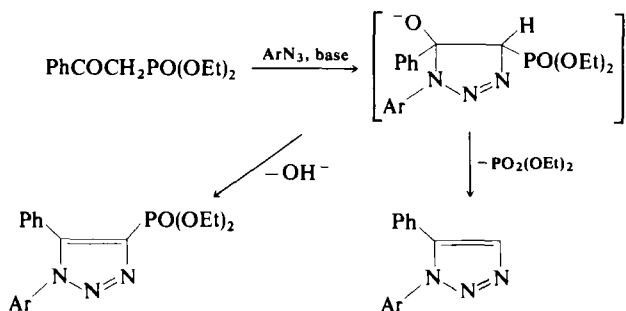
<sup>426</sup> G. L'abbé and A. Hassner, *J. Heterocycl. Chem.* **7**, 361 (1970).

<sup>427</sup> M. Kovačič, S. Polanc, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.* **11**, 949 (1974).



SCHEME 132

aminotriazole, benzoylmethylene phosphonate reacts with aryl azides leading to two triazoles with the 1,5-diaryl compound as the major product (Scheme 133).<sup>422</sup> However, ethoxycarbonylmethylene phosphonate yields only a diazoamide formed by isomerization of the initially formed 5-hydroxytriazole.<sup>422</sup>



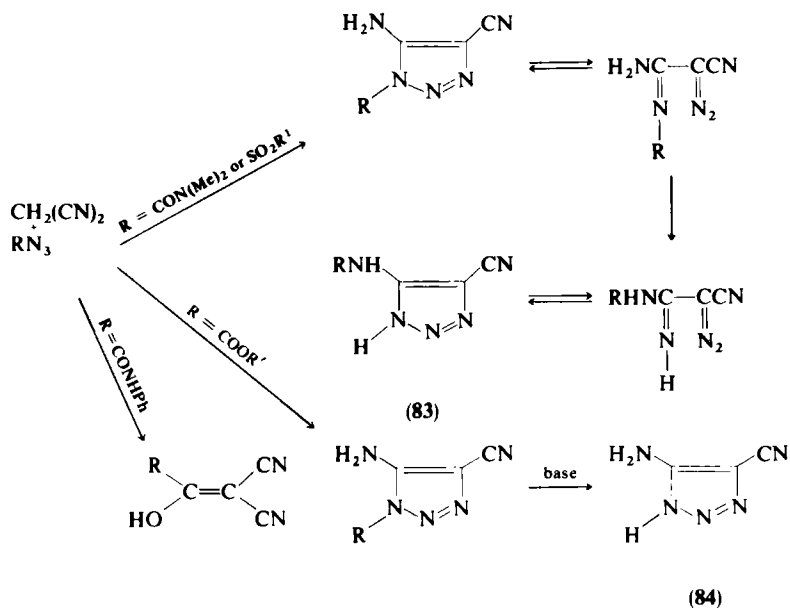
SCHEME 133

Anomalous products have been observed in several cases. Azide addition to malonodinitrile yields a triazole only when the reaction is conducted in aqueous sodium hydroxide solution,<sup>425,428</sup> and the triazoles obtained (**83** and **84**) are determined by the structure of the azide (Scheme 134). The product from the action of phenylcarbamyl azide is not a triazole (Scheme 134).<sup>425</sup> Methylmalononitrile and tosyl azide lead to fragmentation products of the triazole such as imidazolone.<sup>429</sup>

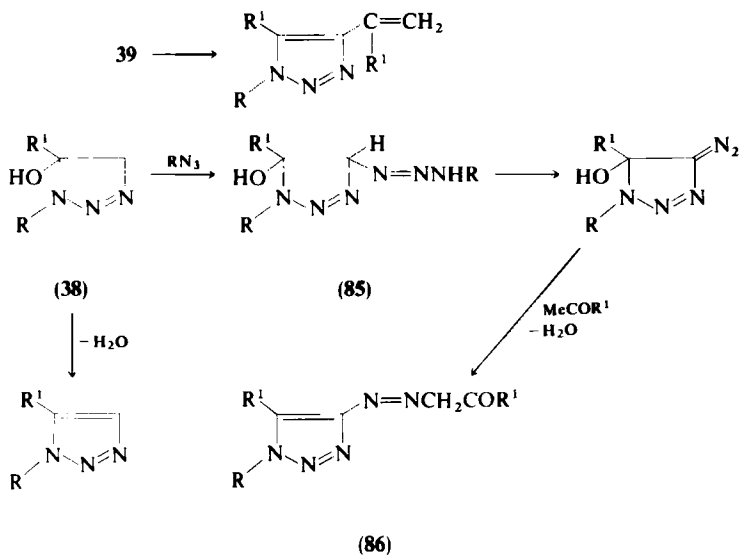
Methyl ketones lead to different triazoles, depending on the azide and ketone employed (Scheme 135).<sup>255</sup> Reaction of benzyl azide with acetone and acetophenone yields mostly one or both of the triazoles derived from **38** and **39** in Scheme 64. Methyl *t*-butyl ketone gives, in addition, a 4-triazenyl-

<sup>428</sup> D. Stadler, W. Auschuetz, M. Regitz, G. Keller, D. Van Assche, and J. P. Fleury, *Liebigs Ann. Chem.*, 2159 (1975).

<sup>429</sup> J. P. Fleury, G. Keller, and B. Libis, *Tetrahedron Lett.*, 751 (1974).



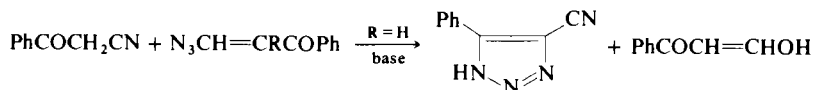
SCHEME 134



SCHEME 135

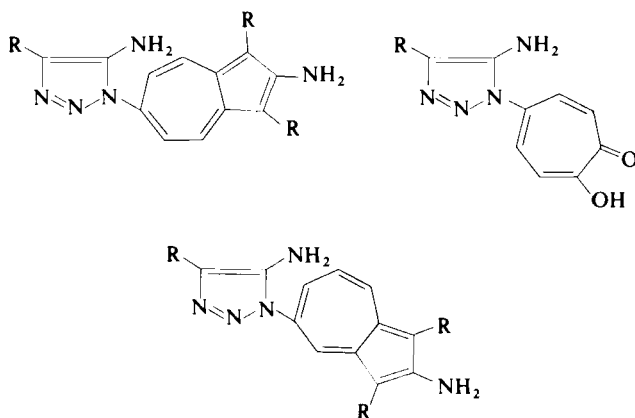
triazoline (**85**). With phenyl azide, however, further reaction with **38** occurs, leading to a new triazole (**86**), which dominates in the acetone reaction.

Vinyl azides lead to triazoles unsubstituted on N-1, when R is hydrogen (Scheme 136).<sup>420</sup>



SCHEME 136

5-Azidotropolone and its methyl ether and tosylate react with active methylene compounds to yield tropolones and azulenes bearing the triazole ring as a substituent (Scheme 137).<sup>419</sup>

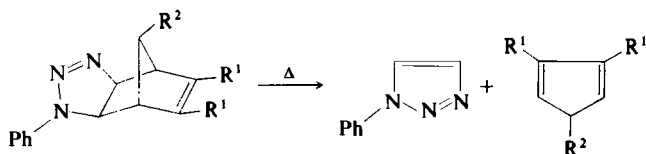


SCHEME 137

## 5. Retro Diels–Alder Reactions

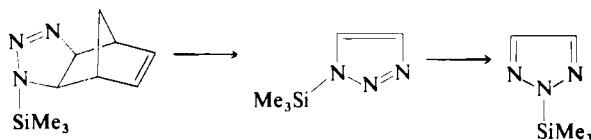
There are several cases of polycyclic triazolines, obtained by azide addition to the strained olefinic bond in bi- and tricyclic systems, that are susceptible to retro Diels–Alder reaction to yield 1-substituted triazoles. A well-established example is the monoadduct from norbornadiene and phenyl azide, which decomposes at 90–100°C to give 1-phenyltriazole and a cyclopentadiene (Scheme 138).<sup>25,97–99,147,430</sup> Similarly, the cycloadduct from the reaction of 7-oxabenzonorbornadiene and 1-azidoadamantane, when heated at 110°C, affords good yields of 1-(1-adamantyl)-1,2,3-triazole in a retro Diels–Alder reaction.<sup>155</sup>

<sup>430</sup> K. Alder and W. Trimborn, *Justus Liebigs Ann. Chem.* **586**, 58 (1950).



SCHEME 138

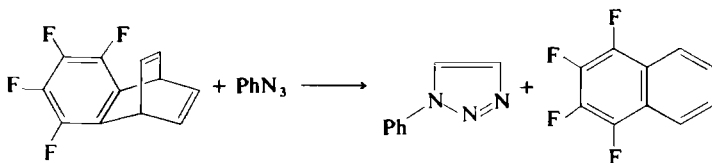
The monoadduct from norbornadiene and the bulky trimethylsilyl azide is less stable than the bisadduct and spontaneously yields a 1-silylated triazole that isomerizes to a 2-silyl triazole (Scheme 139).<sup>104</sup>



SCHEME 139

Diels–Alder type of cycloreversions are frequently observed among the azide adducts from barrelenes. The triazoline reaction product from phenyl azide and tetrafluorobenzobarrelene has never been isolated because of the ease with which it undergoes cycloreversion (Scheme 140).<sup>166</sup> A similar reaction occurs with 1,4-diphosphabarrelene (see Scheme 23)<sup>167,168</sup> as well as with the ethylazidoformate adduct of tetrafluorobenzodihydrobarrelene.<sup>169</sup>

The diphosphabenzvalene–phenyl azide adduct (Scheme 22) undergoes a similar retro addition when treated with silica gel to yield 1-phenyl-4,5-bis(trifluoromethyl)-1,2,3-triazole; the fate of the diphosphabicyclobutane part, however, is not clear.<sup>165</sup>

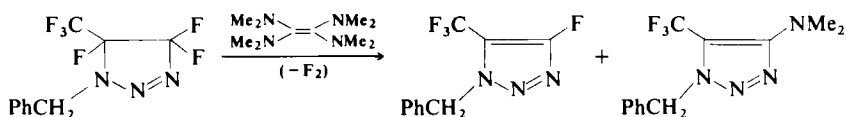


SCHEME 140

## 6. Catalytic Elimination of Fluorine from Fluorinated Triazolines

Although fluorinated triazolines exhibit unusual thermal stability,<sup>145</sup> fluorine elimination can be effected under the influence of tetrakisdimethylaminoethylene as a catalyst (Scheme 141).<sup>145</sup>



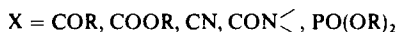
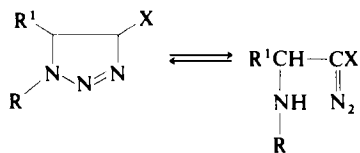


SCHEME 141

## B. FORMATION OF DIAZO COMPOUNDS

### 1. Isomerization to Ring-Opened Diazo Compounds

Triazolines bearing an electron-withdrawing group at C-4 along with a free hydrogen isomerize to give ring-opened diazo compounds either spontaneously<sup>67,159–161,282–284</sup> or under the action of a base<sup>32,278,282,288,304</sup> in an equilibrium reaction resembling the Dimroth rearrangement of 5-amino and 5-hydroxytriazoles (Scheme 142).<sup>285</sup> When R<sup>1</sup> is aromatic<sup>284</sup> and X is an acyl or ester group,<sup>32,284</sup> formation of a diazo compound is favored in the azide-olefin addition reaction (see Scheme 69 and Table I). Olefins substituted by three electron-withdrawing groups yield in some cases a triazoline and an open-chain diazo isomer, indicating addition in both directions (Scheme 85).<sup>282</sup> Triazolines in which R is a heterocyclic substituent (Scheme 70) also undergo facile ring opening with triethylamine.<sup>286,287</sup>

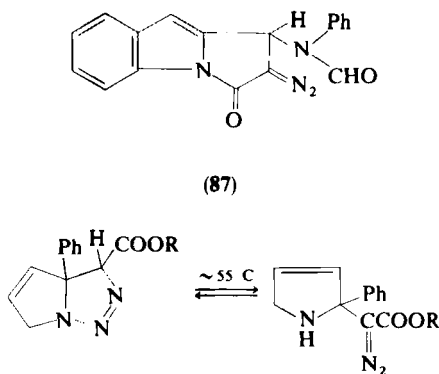


SCHEME 142

The triazoline  $\rightleftharpoons$  diazo compound equilibrium may be considered to play a role in the cis-trans isomerization<sup>332</sup> and oxidation (Scheme 119)<sup>284</sup> of certain triazolines. Triazole formation by elimination of amine<sup>214</sup> or alcohol<sup>405</sup> is also postulated to involve intermediate diazo compounds (Scheme 123). Unlike normal triazolines, the inability of 1-fluorotriazolines to undergo thermolysis or photolysis reactions to yield aziridines is ascribed to the fact that the triazoline always exists in equilibrium with the diazo compound (Scheme 98).<sup>356</sup> Spontaneous isomerizations of triazolines not

bearing an electron-withdrawing X group in the 4-position are also known (Scheme 68).<sup>272,273,405</sup>

Two examples of the conversion of fused-ring triazolines to open-chain diazo isomers are reported. Whereas spontaneous thermal isomerization occurs in a pyrrolotriazoline (Scheme 143),<sup>302</sup> isomerization of the tetracyclic triazoline in Scheme 73 is achieved by the action of phosphorus oxychloride in DMF solution through a Vilsmeier formylation reaction (87).<sup>290</sup>



SCHEME 143

## 2. Retro-1,3-Cycloadditions

An unusual course of thermolysis occurs in 5-amino- and 5-alkoxytriazolines, which are formed only as intermediates in the reaction of enamines and enol ethers with azides bearing electron-withdrawing groups; it involves cleavage of the N-1/N-2 as well as the C-4/C-5 bonds of the triazoline ring to yield diazoalkanes and imines with one fewer carbon than in the triazolines (amidines and imino ethers) (Scheme 144).<sup>233,250,272,431-435</sup> in a cycloelimination reaction, the reverse of diazoalkane-imine cycloaddition. The intermediate formation of a diazonium zwitterion is suggested,<sup>233,247</sup> but whether the thermolysis occurs in a one- or two-step reaction is not established.

With unsubstituted vinyl amines<sup>233,247</sup> and ethers,<sup>233,436</sup> diazomethane is formed and expelled from the reaction but provides a route for amidine and

<sup>431</sup> D. Pocar and R. Stradi, *Ann. Chim. (Rome)* **61**, 181 (1971).

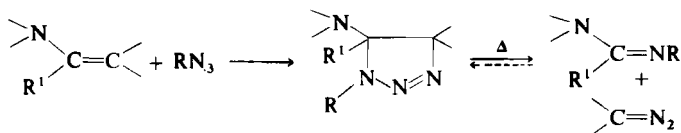
<sup>432</sup> Z. Arnold, *Chem. Commun.*, 299 (1967).

<sup>433</sup> J. Kucera and Z. Arnold, *Tetrahedron Lett.*, 1109 (1966).

<sup>434</sup> J. Kucera, Z. Janousek, and Z. Arnold, *Collect. Czech. Chem. Commun.* **35**, 3618 (1970).

<sup>435</sup> M. Regitz and F. Mens, *Chem. Ber.* **101**, 2622 (1968).

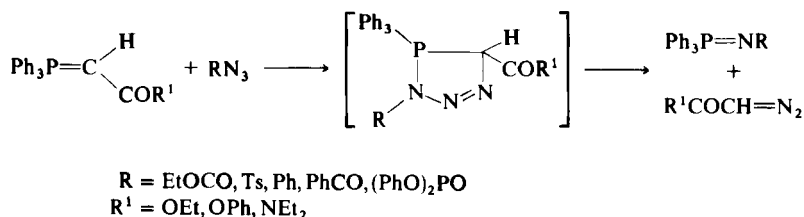
<sup>436</sup> K. D. Berlin and M. A. R. Khayat, *Tetrahedron* **22**, 975 (1966).



SCHEME 144

imino ether synthesis. Reaction of vinyl ether with arylsulfonyl azides leads to a complex mixture of products including an alkoxyamine polymer<sup>174,437-440</sup>, a similar complex reaction also occurs with tetramethoxyethylene.<sup>274,275</sup>

The reaction of dienamines and sulfonyl azides provides a method for the synthesis of vinyldiazomethanes.<sup>233,431</sup> Likewise, the pyrolysis of a fluorinated 1-benzyltriazoline over a nickel surface yields difluorodiazomethane.<sup>145</sup> The formation of diazo compounds from the reaction of azides with alkylidene phosphoranes apparently originates from an intermediate triazoline compound (Scheme 145).<sup>408,411,412,415,441</sup>



SCHEME 145

Thermolysis of spirotriazolines (Schemes 35 and 36) is also postulated to involve retro-1,3-addition with aryldiazomethane expulsion (see Scheme 172 below).<sup>193,194</sup>

Fused-ring triazolines derived from 3,3-dimethylcyclopropene dicarboxylate,<sup>442</sup> Dewar thiophene (as was shown in Scheme 20)<sup>161</sup> and cyclobutadiene undergo thermal isomerization to diazoimino compounds in a retro-1,3-cycloaddition (Scheme 146).

<sup>437</sup> J. E. Franz, M. W. Dietrich, A. Henshall, and C. Osuch, *J. Org. Chem.*, **31**, 2847 (1966).

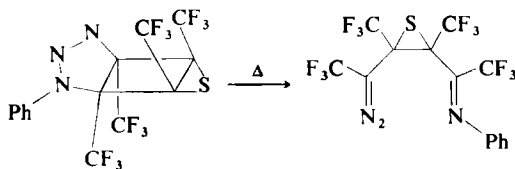
<sup>438</sup> M. A. R. Khayat and F. S. Al Isa, *Tetrahedron Lett.*, 1351 (1970).

<sup>439</sup> K. A. Oglobin, V. P. Semenov, I. K. Khurkovitch, and I. M. Stroiman, *Zh. Org. Khim.* **9**, 263 (1973).

<sup>440</sup> V. P. Semenov, L. V. Volkov, and K. A. Oglobin, *Zh. Org. Khim.* **9**, 2119 (1973).

<sup>441</sup> M. B. Sohn, M. Jones, Jr., M. E. Hendrick, R. R. Rando, and W. E. Doering *Tetrahedron Lett.*, 53 (1972).

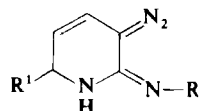
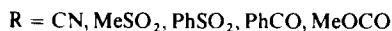
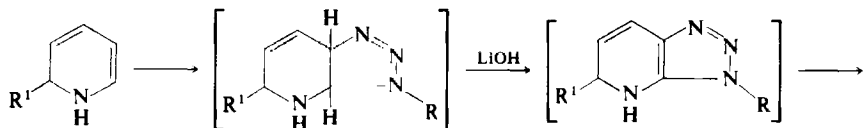
<sup>442</sup> M. F. Neumann and G. Buchecker, *Tetrahedron Lett.*, 2659 (1969).



SCHEME 146

*N*-Methylindole acts like an enamine with sulfonyl azides and gives a diazoimino compound.<sup>443-445</sup> So does dihydropyridine but only in the presence of 5% lithium hydroxide (Scheme 147).<sup>242</sup> A triazole is postulated to be formed from the triazoline followed by a ring opening; oxidation of diazoamino compounds to triazoles has been known to proceed via a diazoimino compound in equilibrium with the triazole (Scheme 119).<sup>285,399,400</sup>

The cycloaddition of azide to olefin can also be reversible<sup>193,240,250,292,446</sup> but of no synthetic value because the starting materials are simply reformed.<sup>240</sup>



SCHEME 147

### 3. Diazo Transfer Reactions

When active methylene compounds in basic medium react with tosyl azide, triazoles are never formed (Section IV,A,4), but the unstable triazoline intermediate undergoes a diazo transfer reaction in a Dimroth-type rearrangement.<sup>447</sup> A typical example is the addition of tosyl azide to a 1,3-diketone

<sup>443</sup> A. S. Bailey, A. J. Buckley, W. A. Warr, and J. J. Wedgwood, *J.C.S. Perkin I*, 2411 (1972).

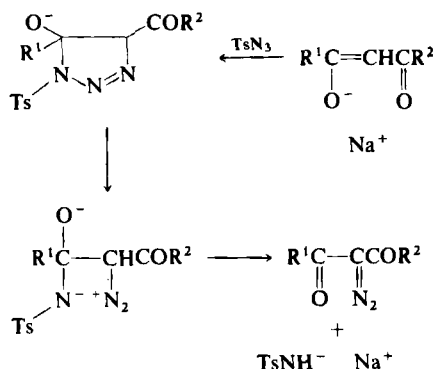
<sup>444</sup> R. E. Harmon, G. Wellman, and S. K. Gupta, *J. Heterocycl. Chem.* **9**, 1193 (1972).

<sup>445</sup> R. E. Harmon, G. Wellman, and S. K. Gupta, *J. Org. Chem.* **38**, 11 (1973).

<sup>446</sup> M. S. Quali, M. Vaultier, and R. Carrie, *Bull. Soc. Chim. Fr.*, 633 (1979).

<sup>447</sup> M. Regitz, *Angew. Chem., Int. Ed. Engl.* **6**, 733 (1967).

(Scheme 148). The tosyl group induces ring opening, in preference to hydroxide elimination, to give a triazole. Numerous diazo esters and ketones have been prepared by diazo transfer reactions<sup>441,447-451</sup> and improved yields obtained using phase-transfer catalysis.<sup>452</sup> Diazoalkane formation via retro-1,3-cycloadditions may also be considered as diazo transfer reactions.<sup>12</sup>



SCHEME 148

## C. REACTIONS CONSEQUENTIAL TO DIAZO COMPOUND FORMATION

### 1. *Pyrazoline Formation*

Spontaneous isomerization of triazolines to diazo compounds can lead to addition of the latter to a second molecule of olefin, especially in the case of acrylic derivatives, resulting in a  $\Delta^1$ -pyrazoline, which by prototropic rearrangement, gives the  $\Delta^2$ -compound (Scheme 149). Pyrazolines have been observed in the reactions of alkyl,<sup>67</sup> aryl,<sup>32,282</sup> heterocyclic,<sup>283,453</sup> and glycosyl<sup>288</sup> azides. A  $\Delta^1$ -pyrazoline is reported from the addition of phenyl and tosyl azides to 3,3-dimethylcyclopropene; in this case the diazoimine formed by a retro-1,3-addition of the primary cyclopropanotriazoline adduct reacts with another olefin molecule.<sup>82</sup>

<sup>448</sup> J. B. Hendrickson and W. A. Wolf, *J. Org. Chem.* **33**, 3610 (1968).

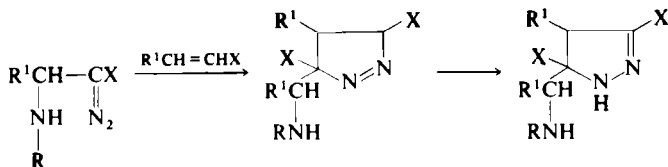
<sup>449</sup> M. Regitz, *Synthesis*, 351 (1972).

<sup>450</sup> M. Regitz, J. Hocker, and A. Liedhegener, *Org. Prep. Proced.* **1**, 99 (1969).

<sup>451</sup> M. Rosenberger, P. Yates, J. B. Hendrickson, and W. Wolf, *Tetrahedron Lett.*, 2285 (1964).

<sup>452</sup> H. Ledon, *Synthesis*, 347 (1974).

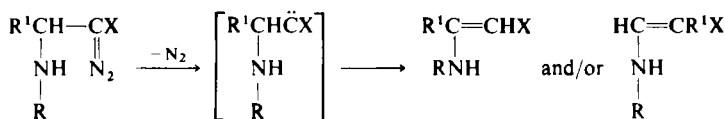
<sup>453</sup> B. Stanovnik, *J. Heterocycl. Chem.* **8**, 1055 (1971).



SCHEME 149

## 2. Formation of Enamines

Enamine formation occurs by the thermolysis of diazo compounds (Scheme 150)<sup>67,109,278,284,288,304,332,453,454</sup> via a carbene-like intermediate.<sup>284,332</sup> When  $\text{R}^1 = \text{Ph}$ , it enters into competition with hydrogen migration,<sup>284,332</sup> and the electrophilic character of the carbene enhances the migration of the dimethylaminophenyl more than the phenyl.<sup>332</sup> When triazoline synthesis is carried out at temperatures higher than that at which thermolysis of diazo compounds occurs, enamines are obtained exclusively, as in the addition of phenyl azide to cinnamic nitriles and ketones, with phenyl migration dominating in the nitrile.<sup>284</sup> Enamine is also formed quantitatively in the reaction of ethyl diazoacetate with benzylideneaniline at  $110^\circ\text{C}$ .<sup>455</sup>



SCHEME 150

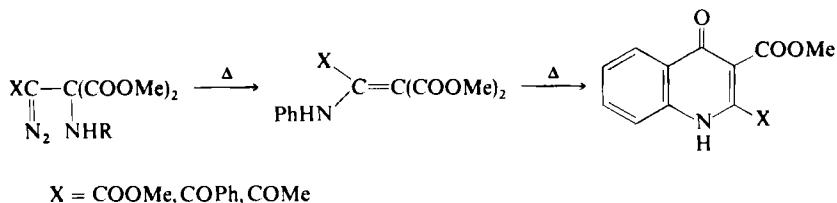
In some cases, depending on the reaction temperature, direct thermolysis of triazolines to aziridines enters into competition with the ring opening to diazo compounds (Scheme 142)<sup>284</sup>; thus thermolysis of 1,5-diaryl-4-cyanotriazolines gives a mixture of aziridines and enamines, the latter resulting from exclusive phenyl migration (Scheme 150).<sup>332</sup> Base-catalyzed decompositions of the triazolines, however, lead only to enamines.<sup>282,332</sup> Hydrogen migration dominates in an enamine postulated to be formed by the opening of the C—N bond of *cis*-1,2-diaryl-3-cyanoaziridine.<sup>332</sup>

## 3. Formation of Quinolines

Certain enamino esters cyclize at high temperatures to quinolines (Scheme 151).<sup>282</sup>

<sup>454</sup> G. Szeimies and R. Huisgen, *Chem. Ber.* **99**, 491 (1966).

<sup>455</sup> A. J. Speziale, C. C. Tung, K. W. Ratts, and A. Yao, *J. Am. Chem. Soc.* **87**, 3460 (1965).



SCHEME 151

### D. RING CLEAVAGE WITH NITROGEN EXPULSION

Triazoline ring cleavage with nitrogen expulsion can be achieved by photolysis or thermolysis and leads to aziridines, imines, or the isomeric enamines.<sup>12</sup> In contrast to thermolysis where product mixtures are obtained, photolysis is more selective and aziridine is the major product.<sup>27,79,252,290</sup>

#### 1. Photolysis

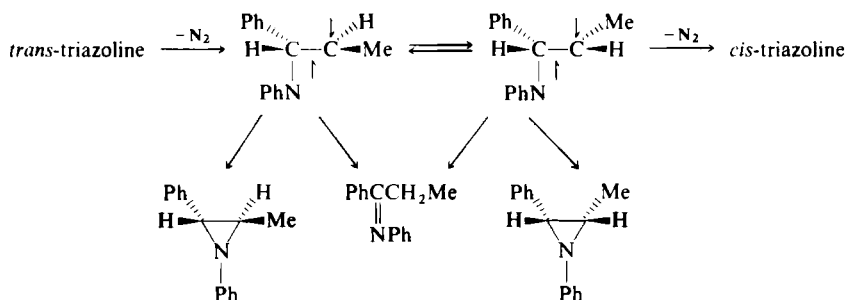
Irradiation of triazolines with UV light of  $\lambda > 240$  nm, the region of maximum absorption, constitutes one of the principal methods for the synthesis of various substituted aziridines.<sup>79,113</sup> The photolysis reaction is essentially independent of substituent and solvent effects; in some cases aziridines are accompanied by imines.<sup>79</sup>

Although aziridine formation is not stereospecific, a predominant retention of the triazoline geometry is observed<sup>27,87</sup>; triplet quenchers fail to modify the reaction and photosensitization leads to loss of specificity.<sup>27,87</sup> Extensive studies on the mechanism of triazoline photolysis<sup>27,87,144,221</sup> have led to the formulation of a singlet 1,3-diradical mechanism (Scheme 152). The high retention of geometry is attributed to the rapidity of ring closure as compared to rotation, and the rotational freedom about the C—C bond determines the extent of imine production. Thus the yield of *exo*-aziridine obtained from the fused-ring triazoline (Scheme 4) is almost quantitative, whereas 17% imine accompanies the aziridine from 4,5,5-trimethyltriazoline.<sup>79</sup>

Numerous aziridines have been prepared by triazoline photolysis; it is the principal route to the synthesis of *N*-arylaziridines. Photolysis of triazolines derived from simple<sup>79,113,144</sup> and cyclic<sup>79,87,113</sup> olefins as well as norbornene and derivatives<sup>25,79,112–114,124,128,130,149,456,457</sup> has been effected; as a rule, the *exo*- and *endo*-triazoline adducts yield the respective *exo*- and *endo*-

<sup>456</sup> O. E. Edwards, J. W. Elder, M. Lesage, and R. W. Retallack, *Can. J. Chem.* **53**, 1019 (1975).

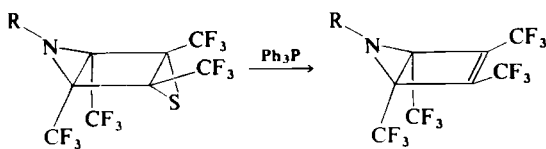
<sup>457</sup> R. S. McDaniel and A. C. Oehlschlager, *Tetrahedron* **25**, 1381 (1969).



SCHEME 152

aziridines.<sup>99,373</sup> Photolysis also affords vinylaziridines,<sup>79,458</sup> N-heterocyclic-substituted 2-vinylaziridines,<sup>183</sup> and spiroaziridines.<sup>12,171,172</sup> However, photolysis of triazoline adducts from norbornadienes and polycyclic dienes does not give similar results<sup>91,97-99,146-149</sup> and are contradictory in some cases.<sup>97,98</sup> The exceptionally stable fluorinated triazolines (Schemes 29 and 96) undergo slow photolysis,<sup>145</sup> and the 1-fluoro compounds (Scheme 98) fail to photolyze because they exist in equilibrium with the diazo compounds.<sup>356</sup>

The triazoline adducts from benzvalene (Scheme 21)<sup>162</sup> and diphosphabenzvalene (Scheme 22) photolyze to yield novel tetracyclic aziridine ring systems<sup>165</sup> that are valence isomers of azepines,<sup>162</sup> whereas that from Dewar thiophene (Scheme 20) gives a novel tricyclic aziridine that desulfurizes with triphenylphosphine to yield the trifluoromethylated Dewar pyrrole (Scheme 153).<sup>159,160</sup> The stabilization of these strained molecules is attributed to the perfluoroalkyl effect.<sup>159</sup>

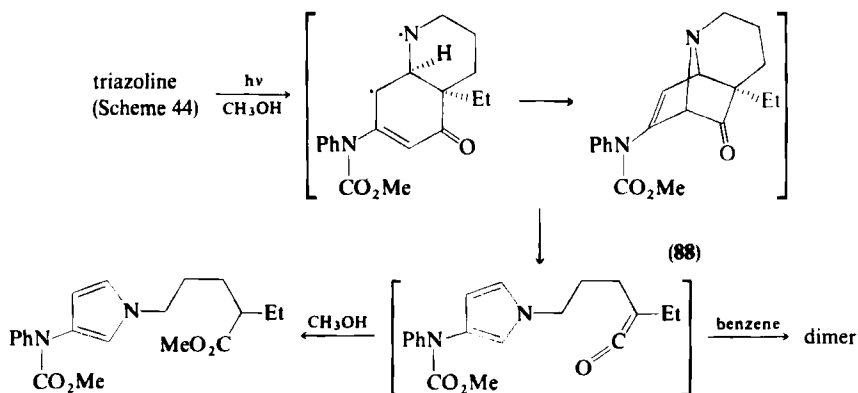


SCHEME 153

A new photoreaction is described for the tricyclic triazoline shown in Scheme 44, which upon irradiation in methanol gives a pyrrole methyl ester<sup>205</sup> by retro Diels–Alder reaction of an intramolecular pyrrole–ketene Diels–Alder adduct (**88**) formed from the diradical (Scheme 154).<sup>205</sup> In benzene, ketene dimerization occurs.

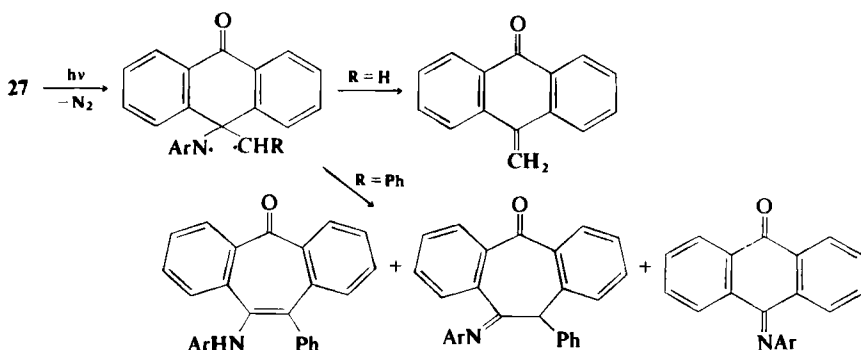
<sup>458</sup> P. Scheiner, *J. Org. Chem.* **32**, 2628 (1967).





SCHEME 154

Photolyses of spiroanthronetriazolines (Scheme 35) are anomalous; they fail to yield aziridines.<sup>193</sup> Complex reaction mixtures are obtained; when the starting quinone methide has  $R = \text{Ph}$ , the aryliminoanthrone and the 10-arylamino (or imino) dibenzotropolones are obtained, but not when  $R = \text{H}$  (Scheme 155). The quinone methide may arise from a photochemical deamination of the diradical, whereas photofragmentation and rearrangement may account for the other products.<sup>193</sup>

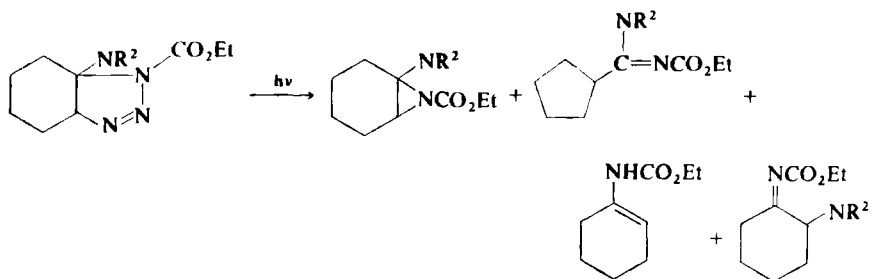


SCHEME 155

The spirofluorenetriazolines (Scheme 36) act similarly; spiroaziridines are not obtained. A complex mixture of products containing 15% of the ring-enlarged 9-arylamino phenanthrene is formed.<sup>194</sup>

Photolysis reactions of 5-amino- or 5-alkoxy-substituted triazolines have not been studied extensively; usually they yield triazoles (Section IV,A,3).

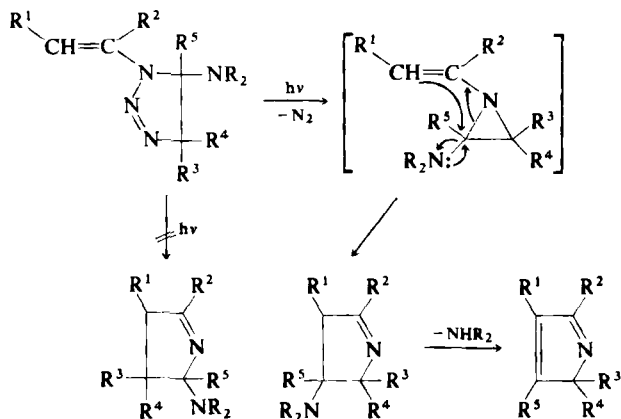
However, when no free hydrogen is present in the 4-position, aziridines, alone<sup>252</sup> or mixed with imines (amidines),<sup>212</sup> are obtained; sometimes more complex mixtures are formed (see, e.g., in Scheme 156).<sup>221</sup>



SCHEME 156

Photolysis of 1-ethoxycarbonyl-5,5-dialkoxytriazolines bearing a 4-alkyl substituent has been found to proceed via 1,3-diradicals, whereas a 1,5 pathway prevails in the absence of 4-substitution.<sup>268</sup> Photolysis of the 4-phenyl compound (see Scheme 68) leads to an oxazole.<sup>404</sup>

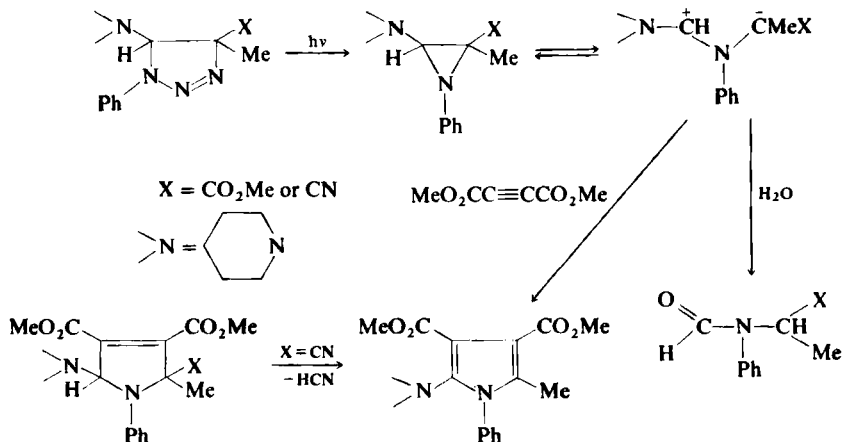
Photoreaction of 1-vinyl-4-alkyl-5-aminotriazolines leads to unexpected pyrrolines and pyrroles.<sup>459</sup> The 1-vinylaziridine formed by ring closure of the 1,3-diradical undergoes a selective ring cleavage at one of the C—N bonds (bearing the amino group) followed by cyclization with the  $\beta$ -vinyl carbon to give the products (Scheme 157).<sup>459</sup>



SCHEME 157

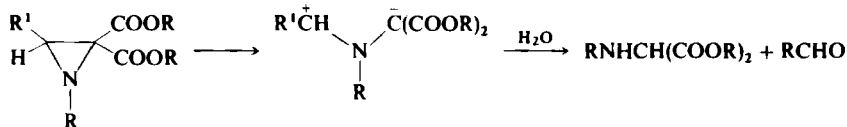
<sup>459</sup> M. M. Ito, Y. Nomura, Y. Takeuchi, and S. Tomoda, *Chem. Lett.*, 1519 (1981).

When the 5-amino- or 5-alkoxytriazoline contains an electron-withdrawing group in the 4-position with no free hydrogen, photolysis leads to unstable aminoaziridines, readily hydrolyzable in air, to give amides via azomethine ylides. In the presence of acetylenedicarboxylic ester, photolysis yields a pyrroline and a pyrrole (Scheme 158).<sup>250</sup>



SCHEME 158

Triazolines bearing an electron-withdrawing nitrile,<sup>79,113,292</sup> amide,<sup>79,460</sup> or ester<sup>292,321</sup> group in the 4-position, usually give quantitative yields of aziridines upon photolysis; the same is true when three electron-withdrawing substituents are present.<sup>446</sup> However, when two ester groups are geminally placed on the 4-carbon, the aziridine hydrolyzes spontaneously to give aminomalonates, apparently via the azomethine ylides (Scheme 159).<sup>321</sup>

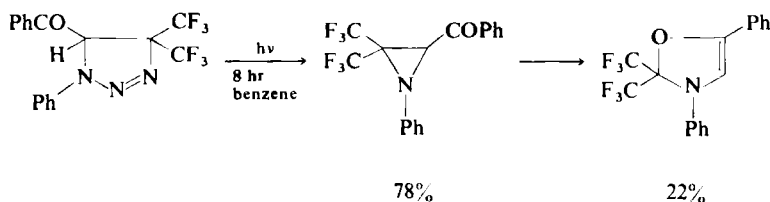


SCHEME 159

Similarly, aziridines resulting from the photolysis of 5-acyl-<sup>292</sup> and 1-acyltriazolines<sup>461</sup> lead to oxazolines (e.g., Scheme 160).

<sup>460</sup> R. W. Franck and K. Bernardy, *J. Org. Chem.* **33**, 3050 (1968).

<sup>461</sup> V. P. Semenov, A. V. Studenikov, and K. A. Oglobin, *Nov. Khim. Karbenov, Mater. Vses. Soveshch. Khim. Karbenov Ikh Analogov, 1st*, 1972, 254 (1973) [*CA* **82**, 49811x (1975)].



SCHEME 160

## 2. Thermolysis

Thermal stability of the triazolines is determined primarily by the electron-withdrawing ability of the N-1 substituent; the more electron withdrawing the substituent is, the greater the ease of triazoline thermolysis.<sup>145</sup> 1-Sulfonyltriazolines have never been isolated<sup>118,170,462-464</sup>; the same applies for the cyano<sup>80a,241,242</sup> and the picryl compounds.<sup>101-103</sup> Aziridines and, to a lesser extent, imines are obtained in place of the triazolines. 1-Acyltriazolines are also labile<sup>9</sup>; but the 1-aryl, heteroaryl,<sup>329-331</sup> and 1-alkyl<sup>79</sup> derivatives are stable for prolonged periods of time under refrigeration. Trimethylsilyl azide adducts of norbornene and norbornadiene are surprisingly stable even at 200°C.<sup>104</sup> The influence of substituents on the ring carbons is less known; however, an electron-donating morpholino substituent on C-5 and C-4 appears to destabilize the triazoline<sup>237</sup> because the isomeric compound with both groups in the C-5 position is sufficiently stable for isolation.<sup>216</sup>

Triazoline thermolysis leads to aziridines, diazo compounds, imines, or enamines; a diazonium betaine is postulated as the intermediate that can undergo stabilization by different pathways,<sup>16,30,80b,112,465</sup> as depicted in Scheme 161. Imine and enamine formation may occur directly from the diazonium betaine<sup>80b,112,226,237,247</sup> or via the diazo compound.<sup>32</sup> Acceleration of the rate of thermolysis of 4,5-dialkyl-substituted triazolines in polar solvents is commensurate with the betaine intermediate,<sup>100,112,457,466</sup> and attempts to prove a 1,3-zwitterionic intermediate have failed.<sup>467-469</sup>

<sup>462</sup> J. E. Franz and C. Osuch, *Tetrahedron Lett.*, 837 (1963).

<sup>463</sup> J. E. Franz and C. Osuch, *Chem. Ind. (London)*, 2058 (1964).

<sup>464</sup> J. E. Franz, C. Osuch, and M. W. Dietrich, *J. Org. Chem.* **29**, 2922 (1964).

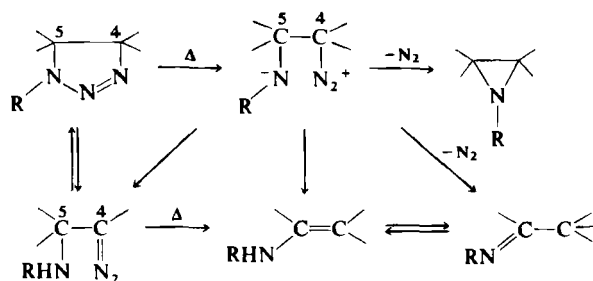
<sup>465</sup> A. C. Oehlschlager and L. H. Zalkow, *Can. J. Chem.* **47**, 461 (1969).

<sup>466</sup> K. D. Berlin, L. A. Wilson, and L. M. Raff, *Tetrahedron* **23**, 965 (1967).

<sup>467</sup> J. E. Baldwin, G. V. Kaiser, and J. A. Romersberger, *J. Am. Chem. Soc.* **87**, 4114 (1965).

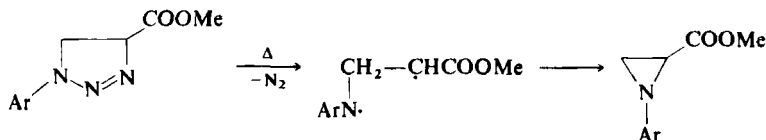
<sup>468</sup> R. Huisgen, R. Grashey, J. M. Vernon, and R. Kunz, *Tetrahedron* **21**, 3311 (1965).

<sup>469</sup> R. A. Wohl, *Helv. Chim. Acta* **56**, 1826 (1973).



SCHEME 161

When electron-withdrawing groups are present on the 4-carbon, triazoline thermolysis is insensitive to solvent polarity; a homolytic decomposition to a singlet diradical similar to that formed in photolysis is proposed to account for the selective formation of aziridine in these cases (Scheme 162).<sup>67,172,454</sup> The lower thermolysis temperatures of *N*-aryltriazolines ( $\sim 25^\circ\text{C}$ )<sup>67,322</sup> as compared to those for the *N*-alkyl compounds ( $\sim 90^\circ\text{C}$ )<sup>67</sup> are consistent with the stabilization of the diradical by aryl groups.



SCHEME 162

Several factors influence product formation in triazoline thermolysis. The stereochemistry of the triazoline adducts from *cis*- and *trans*-cyclooctene has been found to play a role in aziridine or imine formation; aziridines predominate in the *trans* and imines in the *cis* isomers.<sup>86</sup> However, the relative product ratios depend on the reaction temperature, and thermolysis of the *cis*-triazoline at  $310^\circ\text{C}$  leads to 78% aziridine as against 5% at  $80^\circ\text{C}$ .<sup>87</sup>

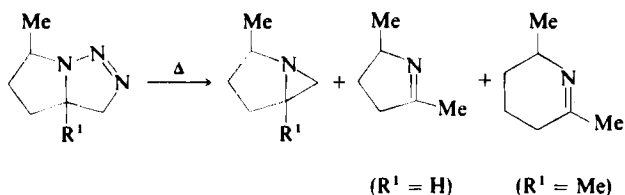
1-Vinyltriazolines are unique; thermolysis leads to high yields of 1-vinylaziridines. This is true of fused-ring tetracyclic (Scheme 40)<sup>199,201</sup> and tricyclic triazolines (Schemes 42 and 43)<sup>200,204</sup> with vinylic substitution in the 1-position. 1-Vinyltriazoline with no substituents on the ring carbons furnishes 1-vinylaziridine without formation of pyrrolines.<sup>378</sup> Thermal decomposition of vinyl azides in acrylic acid derivatives is a synthetic route for 2-substituted 1-vinylaziridines.<sup>470</sup> Similarly, aziridine 1-oximes are the only products of thermolysis of triazoline 1-oximes.<sup>107</sup>

<sup>470</sup> Y. Nomura, N. Hatanaka, and Y. Takeuchi, *Chem. Lett.*, 901 (1976).

Substituents on the ring carbons play an important role in thermolysis; aziridines are seldom formed when an electron-donating group is present on C-5, whereas electron-withdrawing groups on C-4 lead mainly to aziridines with a marked retention of the triazoline geometry (see Scheme 162).<sup>86,87,454</sup> The 5-aminotriazolines derived from 1,2- and 1,4-dihydropyridines and cyanogen azide (Scheme 60) are exceptions; they give quantitative yields of the 1-cyanoaziridines via thermolysis.<sup>241-243</sup>

a. *Triazolines from Simple Olefins.* Thermolysis of triazolines bearing an alkyl or aryl group in the 4- or 5-position, usually leads to a mixture of aziridine and imine.<sup>25,80b,86,112,180,206,466,471-473</sup> Imines predominate in the case of triazolines derived from monocyclic or linear olefins.<sup>80a,91,101-103,109,190-192,206,471,472,474-476</sup> Alkenylsilanes react with silyl azides to give silylenamines.<sup>78</sup> 4-Methylenetriazoline (Scheme 32) gives only the imine by methyl migration.<sup>185</sup> When two different groups are present on C-5, both migrate, and two isomeric imines are obtained.<sup>471</sup>

The migratory aptitude of the substituents in the bicyclic triazoline (Scheme 163) is the same as in the pinacolic rearrangement. In addition to the aziridine, which is always minor, a ring-enlarged imine is formed when  $R^1 = \text{CH}_3$ .<sup>100</sup>



SCHEME 163

The labile triazolines from the addition of sulfonyl azides to simple acyclic and cyclic dienes afford enamines or sulfonimides (imines) depending on whether or not the diene is conjugated. When conjugation is present, nitrogen loss from the betaine intermediate occurs with concerted hydrogen, alkyl, or vinyl migration. Hydrolysis of the sulfonimides provides a route for ketone synthesis.<sup>184</sup>

<sup>471</sup> M. E. Hermes and F. D. Marsh, *J. Org. Chem.* **37**, 2969 (1972).

<sup>472</sup> P. P. Nicholas, *J. Org. Chem.* **40**, 3396 (1975).

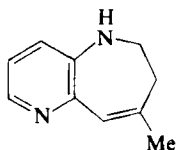
<sup>473</sup> J. W. Bastable, J. D. Hobson, and W. D. Riddell, *J.C.S. Perkin I*, 2205 (1972).

<sup>474</sup> R. A. Abramovitch, G. N. Knaus, M. Pavlin, and W. D. Holcomb, *J.C.S. Perkin I*, 2169 (1974).

<sup>475</sup> W. Ando, H. Fuji, I. Nakamura, N. Ogino, and T. Migita, *Int. J. Sulfur Chem.* **8**, 13 (1973).

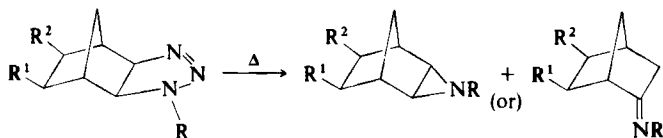
<sup>476</sup> R. E. Banks and G. R. Sparkes, *J.C.S. Perkin I*, 2964 (1972).

Fluorinated triazolines (Scheme 29) are particularly stable and require high temperatures for thermolysis when aziridines are obtained.<sup>145</sup> Thermolysis of aryl-substituted triazolines is not well investigated<sup>144,175</sup>; the 1-*p*-nitrophenyl-5-phenyl compound yields exclusively aziridine, whereas the 1,4-isomer gives the imine as the major product.<sup>175</sup> 1-Heterocyclic-substituted 5-vinyltriazolines (Scheme 31) give 5-vinylaziridines, which undergo thermal isomerization to azepine derivatives (e.g., **89**).<sup>183</sup>



(89)

b. *Fused-Ring Triazolines from Strained Olefins.* Triazoline adducts of *exo* structure, both labile and isolable, from azide addition to norbornene and derivatives (Section II,A,1) sometimes lead to *exo*-aziridine<sup>124,127</sup> or to an imine<sup>105,466,477,478</sup> as the sole product, but in most cases mixtures are formed (Scheme 164).<sup>16,25,29,91,101-103,111,112,117,456,457,462,464,471,476,479</sup> Minor quantities of *endo*-aziridines are also identified.<sup>111,457</sup>



SCHEME 164

In some cases, significant amounts of *endo*-aziridines are formed<sup>106,465,480</sup>; a mechanism involving a C-4/C-5 bond cleavage is proposed (Scheme 165).<sup>106,465</sup>

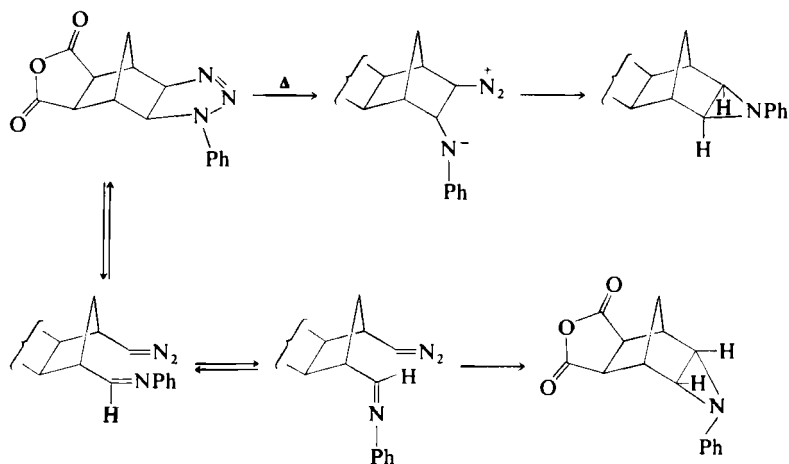
In some thermolysis reactions, amines (**90** and **91**) have been characterized.<sup>108,111,112,457</sup> When  $R^1 = \text{CH}_2\text{OH}$  and  $R^2 = \text{H}$  in Scheme 164, the aziridine undergoes spontaneous rearrangement (Scheme 166).<sup>125</sup> An *endo*-triazoline adduct from norbornene yields a polymer as the principal

<sup>477</sup> K. D. Berlin and R. Ranganathan, *Tetrahedron* **25**, 793 (1969).

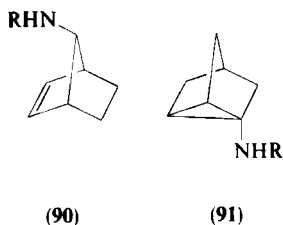
<sup>478</sup> K. D. Berlin and S. Rengaraju, *Tetrahedron* **27**, 2399 (1971).

<sup>479</sup> I. R. A. Bernard, G. E. Chivers, R. J. W. Cremlyn, and K. G. Mootoosamy, *Aust. J. Chem.* **27**, 171 (1974).

<sup>480</sup> L. H. Zalkow and C. D. Kennedy, *J. Org. Chem.* **28**, 3309 (1963).



SCHEME 165



SCHEME 166

decomposition product in addition to the imine and the *endo*- and *exo*-aziridine.<sup>373</sup>

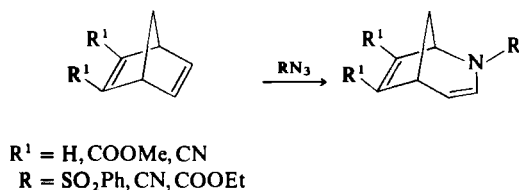
The thermolytic behavior of triazolines formed by the addition of phosphoryl azides to norbornenes differs from related compounds; imines (phosphoramidates) are the sole decomposition products.<sup>105,466,477,478</sup> The rate of decomposition is described by two consecutive first-order reactions, formation of the betaine in the first step and nitrogen expulsion in the



second.<sup>466</sup> Experiments with deuterated molecules indicate no rearrangement in the carbon skeleton.<sup>477</sup> Phosphoryl azide addition to 2-methyl-2-norbornene leads to two imines with the methyl in the *exo* and *endo* positions, migration apparently occurring during thermolysis of the labile triazoline intermediate.<sup>478</sup>

The influence of both anti and syn substitution in the 10-position on the thermolysis of triazoline adducts from a number of 7-substituted norbornenes (Scheme 14) has been investigated.<sup>128</sup> Both the anti- and syn-substituted triazolines give only the *exo*-aziridine upon photolysis; but pyrolysis yields *endo*-aziridines from the *syn*- and *exo*-aziridines from the anti compounds. The *syn* substituents have a strong *endo* directing influence and no *exo*-aziridine is detected in any case. Ketone formation in some cases apparently results from hydrolysis of the imines during workup.<sup>128</sup>

The thermolysis of triazoline adducts from other polycyclic bridgehead olefins is analogous to that of the norbornene-azide adducts (Scheme 164) and affords a route for the synthesis of various aziridine ring systems.<sup>80b,89,91,99,116,117,134,465,471,476,481,482</sup> The addition of benzenesulfonyl azide<sup>80b,463</sup> and cyanogen azide<sup>483</sup> to unsubstituted norbornadiene gives rise to the *exo*-aziridine; but addition to the bismethoxycarbonyl- and biscyano-substituted compounds yields the *endo*-aziridines.<sup>119</sup> Thermal rearrangement of the aziridines leads to normorphan derivatives (Scheme 167).<sup>121</sup>



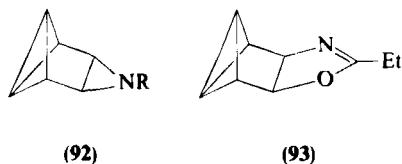
SCHEME 167

The *endo* adduct from dihydrobarrelene and phenyl azide (Scheme 24) yields an *endo*-aziridine on thermolysis.<sup>169</sup> The triazoline adducts from benzvalene (Scheme 21) provide a source for unique aziridines with the azatetracycloheptane ring system (**92**), a new valence isomer of azepine.<sup>162</sup> When  $\text{R} = \text{COOEt}$ , the oxazoline (**93**) is obtained.<sup>162</sup> Thermolysis of triazolines derived from trifluoromethylated diphosphabenzvalene (Scheme 22) gives the corresponding aziridines along with the starting olefin<sup>165</sup>; there is no diazoimine or diphosphazepine formation, which would have resulted from the triazoline to eliminate internal strain.<sup>165</sup>

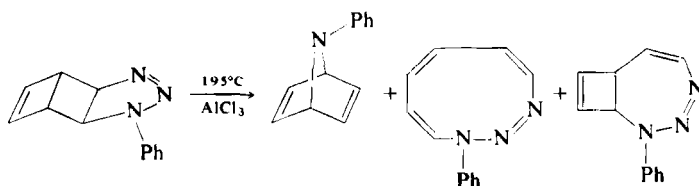
<sup>481</sup> A. C. Oehlschlager and L. H. Zalkow, *Chem. Commun.*, 70 (1965).

<sup>482</sup> A. C. Oehlschlager and L. H. Zalkow, *Chem. Commun.*, 144 (1966).

<sup>483</sup> A. G. Anastassiou, *J. Org. Chem.* **31**, 1131 (1966).



The primary adducts from the reaction of tetrachlorocyclopropene and azides yield chlorinated azabutadienes.<sup>170b</sup> The triazoline derived from Dewar benzene and phenyl azide, when heated in the presence of aluminum chloride, yields unique ring-enlarged heterocycles (Scheme 168).<sup>484</sup>



SCHEME 168

c. *Triazolines from Intramolecular Cycloaddition.* Intramolecular olefin-azide additions lead to thermally labile fused-ring triazolines (Section II,A,2,c), and the reaction products of vinyl (see Scheme 37) and allyl azides are, in fact, thermolysis products of the intermediate triazolines.<sup>100</sup>

*o*-Vinyl and allylazetidide azides when heated give a mixture of two imines or enamines (Scheme 169).<sup>485</sup>

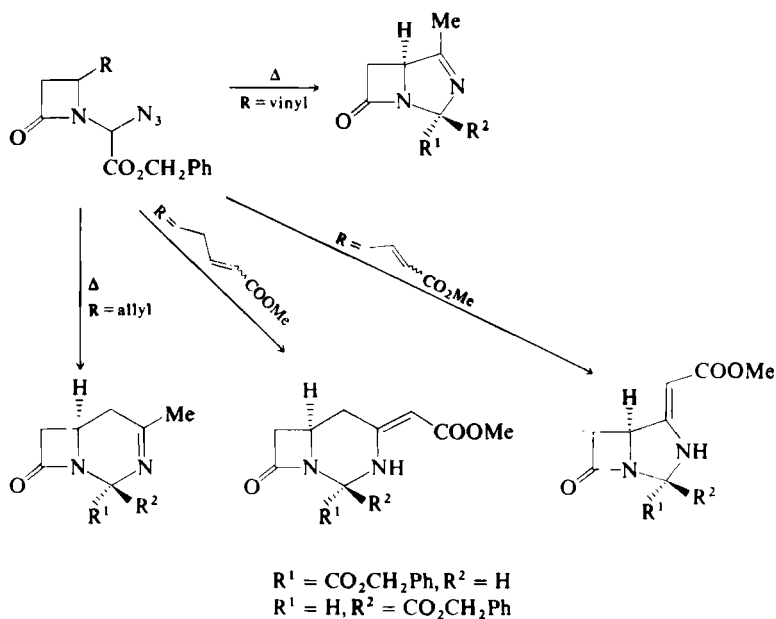
Heterocyclic-substituted vinyl azides lead to pyrrole derivatives (Scheme 170).<sup>486</sup>

The facile decomposition of *o*-allyloxyphenyl azides to give dihydroazirinobenzoxazines occurs via thermolysis of the intermediate triazolines (Scheme 38)<sup>196,197</sup>; when  $R^1 = R^2 = H$ , benzoxazines (imines) (94) are also formed.<sup>196,197</sup> Azides bearing methyl substituents on the terminal olefinic carbon yield, in addition to the expected aziridine and imine, a new product, 3-alkenylbenzomorpholine (95).<sup>197</sup> Azides bearing cycloalkenyl groups (e.g., Scheme 39) give aziridines as the only detectable simple products.<sup>197</sup> A study of the product-determining factors including stereochemical considerations indicates a zwitterion or diradical as the common intermediate.<sup>197</sup>

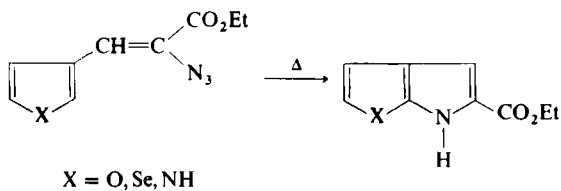
<sup>484</sup> L. A. Paquette and R. J. Haluska, *J. Am. Chem. Soc.* **94**, 534 (1972).

<sup>485</sup> C. L. Branch and M. J. Pearson, *Chem. Commun.*, 946 (1981).

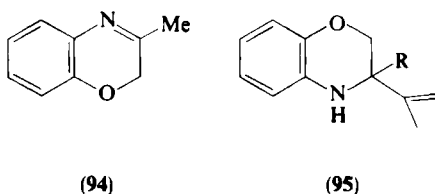
<sup>486</sup> K. N. Java, S. Soth, M. Farnier, and C. Paulmier, *C.R. Hebd. Seances Acad. Sci., Ser. C* **281**, 793 (1975).



SCHEME 169



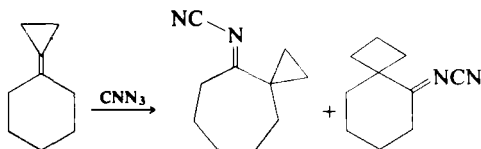
SCHEME 170



d. *Spirotriazolines*. Thermolytic decomposition of spirotriazolines (Section II,A,2,b) fails to yield aziridines as does photolysis; generally ring-enlargement reactions occur via diazonium zwitterionic intermediates leading

to ring-expanded imine compounds in good yields, which upon hydrolysis provide a useful route to cyclic ketones.<sup>187,190,191</sup>

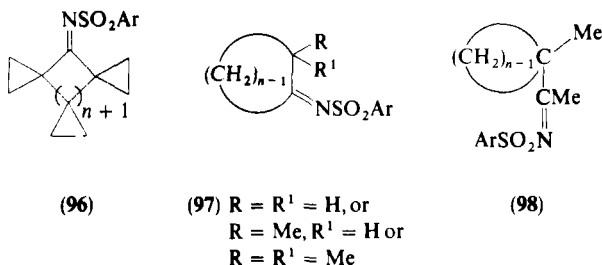
Two ring-enlarged imines are obtained from the two modes of addition of cyanogen azide to cyclopropylidenecyclohexane with weak double-bond



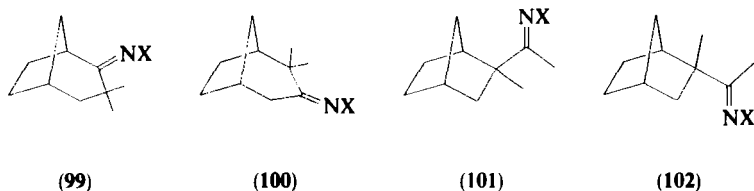
SCHEME 171

dissymmetry (Scheme 171).<sup>191</sup> A similar reaction occurs during the thermolysis of the spirocyclic olefin-azide adduct in Scheme 34, and the sulfonimide (**96**) is the product.<sup>188,189</sup>

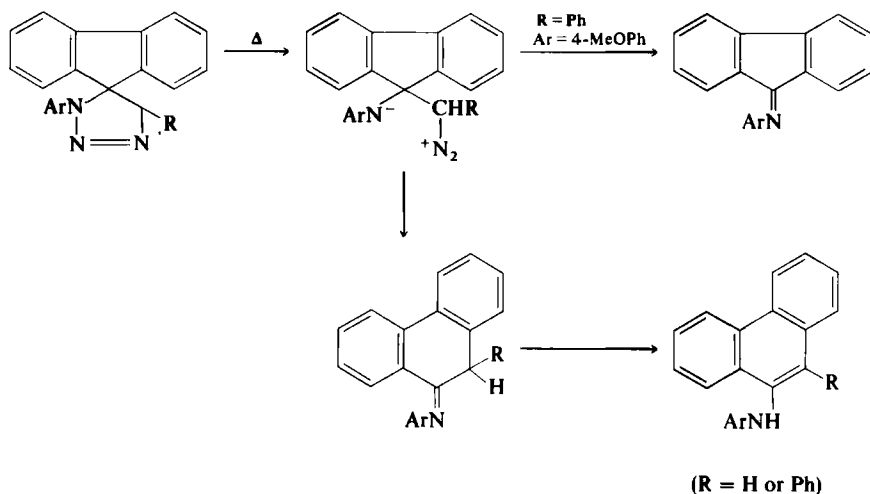
Similarly, spirotriazoline intermediates from the addition of *p*-nitrobenzenesulfonyl azide to exocyclic olefins **22** and **23** give a single ring-expanded sulfonimide (**97**),<sup>187,190-192</sup> whereas those derived from **24** yield two sulfonimides, **97** from ring expansion and **98** from methyl migration.<sup>187</sup> Four



sulfonimides (**99**, **100**, **101**, and **102**) result from **25**, corresponding to the four triazoline adducts from the four possible modes of azide addition.<sup>187</sup>



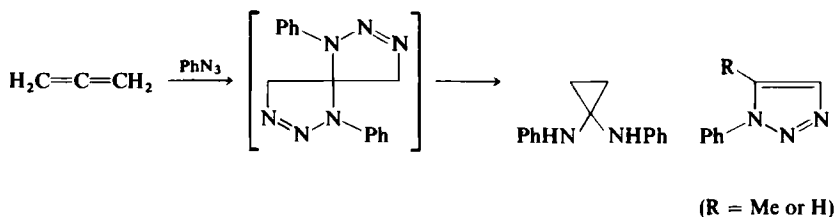
The regioselective spirofluorenetriazolines decompose to yield 9-arylaminophenanthrenes; when  $R = Ph$ , aryliminofluorenes are also formed (Scheme 172).<sup>194</sup>



SCHEME 172

Spiroanthronetriazolines (**27**, Scheme 35) undergo strikingly similar thermolysis reactions via the corresponding diazonium zwitterion; aryliminoanthrones (when Ar = 4-MeOPh and R = Ph in **27**) and ring-enlarged dibenzotropolones, the same as those in photolysis, (Scheme 155) are obtained.<sup>193</sup> In addition, unlike the spirofluorenetriazolines, **27** undergoes extensive thermal cycloreversion to the starting quinone methide and azide.<sup>193</sup>

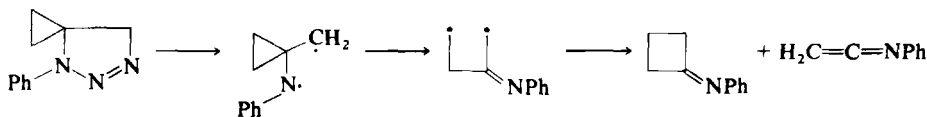
The formation of geminal diaminocyclopropane from the addition of phenyl azide to allene presumably proceeds through an intermediate spirobistriazoline (Scheme 173).<sup>486a</sup>



SCHEME 173

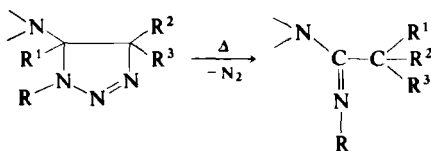
The spirocyclopropanetriazolines are exceptions; a diradical mechanism is proposed (Scheme 174).<sup>172</sup>

<sup>486a</sup> R. K. Khattak, *Diss. Abstr. Int. B* **35**, 3247 (1975).



SCHEME 174

e. *5-Aminotriazolines*. 5-Aminotriazolines, not including those from cyclic enamines,<sup>39</sup> usually lead to triazoles under the influence of heat (Section IV,A,3,a); aziridines are never formed. The formation of amidines with one fewer carbon than in the triazolines has been discussed (Section IV,B,2). However, with highly electron-withdrawing azides, nitrogen elimination from all labile 5-aminotriazolines gives rise to amidines (imines) with the same number of carbon atoms as in the triazoline (Scheme 175).<sup>30,39,208,221,223,225,239,487-490</sup> The triazoline gives amidines only when  $R^1 = H$  and  $R^2 = \text{alkyl}$ ; if  $R^1 = \text{alkyl}$ , amidine formation occurs only when R is highly electron withdrawing and the 5-amino group is tertiary. When  $R^1 = \text{aryl}$ , the amidines lead to  $\alpha$ -arylalkanoic acids upon hydrolysis<sup>491</sup>; the nonsteroidal antiinflammatory agents, ibuprofen and naproxen, have thus been synthesized.<sup>491</sup>



SCHEME 175

Amidines are also formed from less stable 1-hetaryl-<sup>220</sup> and 1-styryl-5-aminotriazolines.<sup>222,492,493</sup> Thermolysis of the latter provides a method of synthesis of novel 1-amino-2-azabutadienes (Scheme 176).<sup>492,493</sup>

Whereas cyanogen azide addition to dihydropyridines leads to bicycloaziridines,<sup>241-243</sup> addition of ethyl azidoformate yields the corresponding amidine.<sup>494</sup> Likewise, indoles (**103**) react with picryl and sulfonyl azides to give

<sup>487</sup> K. D. Berlin and L. A. Wilson, *Chem. Ind. (London)*, 1522 (1965).

<sup>488</sup> P. D. Croce and R. Stradi, *Rend.—Ist. Lomb. Accad. Sci. Lett., A* **101**, 692 (1967).

<sup>489</sup> D. Pocar and P. Trimarco, *J. C.S. Perkin I*, 622 (1976).

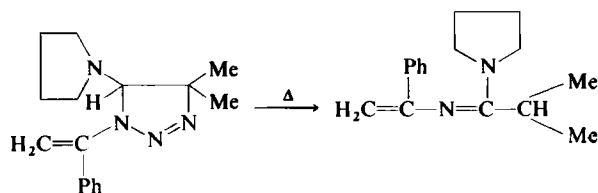
<sup>490</sup> Y. Sato, H. Kojima, and H. Shirai, *J. Org. Chem.* **41**, 3325 (1976).

<sup>491</sup> T. Shioiri and N. Kawai, *J. Org. Chem.* **43**, 2936 (1978).

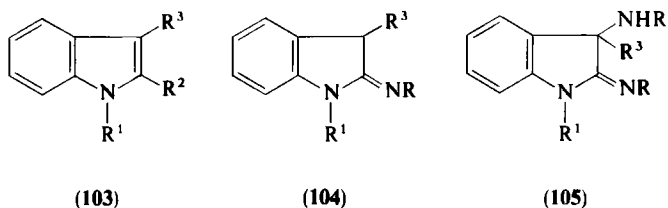
<sup>492</sup> Y. Nomura, Y. Takeuchi, S. Tomoda, and M. M. Ito, *Chem. Lett.*, 187 (1979).

<sup>493</sup> Y. Nomura, Y. Takeuchi, S. Tomoda, and M. M. Ito, *Bull. Chem. Soc. Jpn.* **54**, 2779 (1981).

<sup>494</sup> E. J. Moriconi and R. E. Misner, *J. Org. Chem.* **34**, 3672 (1969).

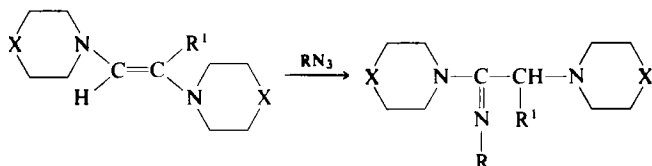


SCHEME 176



amidines (**104**) when  $R^1$ ,  $R^2$ , and  $R^3$  are various combinations of hydrogen, alkyl, and aryl groups.<sup>443–445, 495–501</sup>

Reaction of tosyl<sup>237</sup> and electron-withdrawing aryl azides<sup>207,237</sup> with 1,2-diaminoethylenes provides a route for the synthesis of very high yields of aminoamidines (Scheme 177).<sup>207,237</sup>



$X = O, CH_2$ ;  $R^1 = H, Ph$

SCHEME 177

Aminoamidines (**105**) are also formed from the reaction of picryl and sulfonyl azides with indoles (**103**) when  $R^1$ ,  $R^2$ , and  $R^3$  are all alkyl groups or a

<sup>495</sup> A. S. Bailey and A. J. Buckley, *Tetrahedron Lett.*, 3949 (1972).

<sup>496</sup> A. S. Bailey and A. J. Buckley, *J.C.S. Perkin I*, 1602 (1973).

<sup>497</sup> A. S. Bailey, A. J. Buckley, and W. A. Warr, *J.C.S. Perkin I*, 1626 (1972).

<sup>498</sup> A. S. Bailey, M. C. Churn, and J. J. Wedgwood, *Tetrahedron Lett.*, 5953 (1968).

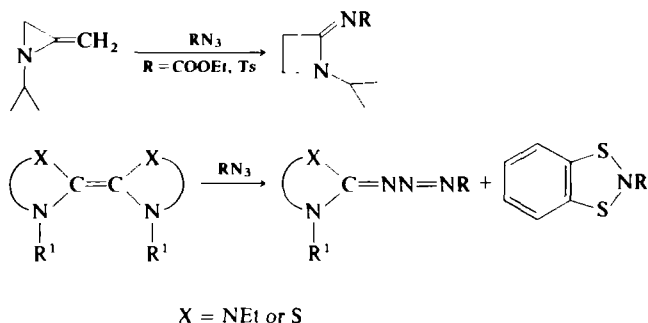
<sup>499</sup> A. S. Bailey, R. Scattergood, W. A. Warr, and T. S. Cameron, *Tetrahedron Lett.*, 2979 (1970).

<sup>500</sup> A. S. Bailey, W. A. Warr, G. B. Allison, and C. K. Prout, *J. Chem. Soc. C*, 956 (1970).

<sup>501</sup> A. S. Bailey, J. F. Seager, and Z. Rashid, *J.C.S. Perkin I*, 2384 (1974).

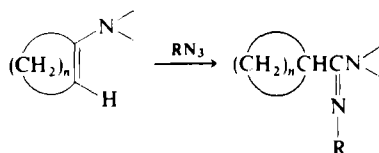
combination of alkyl groups and hydrogen.<sup>496,497,499,502,503</sup> Azide addition to other substituted indoles leads to azoindoles<sup>501,504</sup> and amines,<sup>499,502,503</sup> whereas an indole 2-oxime leads to an oxazole and a hydroxyamidine.<sup>505</sup>

Exocyclic enamines react with azides to give heterocycles (see examples in Scheme 178).<sup>234,506-509</sup>



SCHEME 178

In the case of endocyclic enamines, the imines from the triazoline decomposition are one-carbon, ring-contracted products (Scheme 179).<sup>30,39,225,510,511</sup> Application of the reaction to cholestanonepyrrolidine



SCHEME 179

enamine, using diphenyl phosphorazidate, gives 79% of A-norsteroid.<sup>510</sup> When applied to enolizable imines,<sup>208,225,226</sup> ring contraction is not observed; when  $n = 3$  and  $R = \text{tosyl}$ , a 1,2-diaminoethylene (**106**) is obtained.<sup>36</sup>

<sup>502</sup> A. S. Bailey, R. Scattergood, and W. A. Warr, *J. Chem. Soc. C*, 2479 (1971).

<sup>503</sup> A. S. Bailey, R. Scattergood, and W. A. Warr, *J. Chem. Soc. C*, 3769 (1971).

<sup>504</sup> A. S. Bailey and J. J. Merer, *J. Chem. Soc. C*, 1345 (1966).

<sup>505</sup> A. S. Bailey, C. J. Barnes, and P. A. Wilkinson, *J.C.S. Perkin I*, 1321 (1974).

<sup>506</sup> J. K. Crandall and J. B. Komin, *Chem. Commun.*, 436 (1975).

<sup>507</sup> H. Quast and S. Hunig, *Angew. Chem., Int. Ed. Engl.* **3**, 800 (1964).

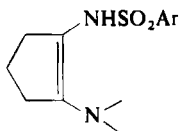
<sup>508</sup> H. Quast and S. Hunig, *Chem. Ber.* **99**, 2017 (1966).

<sup>509</sup> H. E. Winderg and D. D. Coffman, *J. Am. Chem. Soc.* **87**, 2776 (1965).

<sup>510</sup> S. Yamada, Y. Hamada, K. Ninomiya, and T. Shioiri, *Tetrahedron Lett.*, 4749 (1976).

<sup>511</sup> R. M. Scribner, *Tetrahedron Lett.*, 4737 (1967).

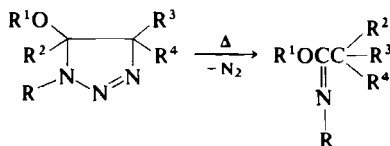




(106)

Indoles (103), where  $R^2R^3$  is a cyclic substituent, react with azides to give ring-contraction or -expansion products, depending on the arylsulfonyl azide and the solvent.<sup>499,502,503,512-517</sup> Dihydroquinolines and dihydroisoquinolines<sup>518</sup> as well as indolizines<sup>519</sup> show analogous behavior.

f. *5-Alkoxytriazolines*. Heat-induced reactions of 5-alkoxytriazolines, including triazole formation (Section IV,A,3,b) and retro-1,3-additions (Section IV,B,2) are analogous to that of the 5-amino compounds; imines that are imino ethers (imide esters) are the products of thermolysis with nitrogen loss (Scheme 180).<sup>26,174,469,520,521</sup> The *cis*-triazolines decompose faster than



SCHEME 180

their *trans* isomers.<sup>26,174</sup> Triazolines resulting from cyclic vinyl ethers (e.g., dihydropyran) yield imino lactones (107) where R can be arylsulfonyl,<sup>39,252,437,522,523</sup> pentafluorophenyl,<sup>206</sup> ethoxycarbonyl,<sup>252,524</sup> heterocyclic,<sup>91</sup> picryl,<sup>504</sup> or aryl.<sup>39,252</sup>

<sup>512</sup> A. S. Bailey, A. J. Buckley, and J. F. Seager, *J.C.S. Perkin I*, 1809 (1973).

<sup>513</sup> A. S. Bailey, P. A. Hill, and J. F. Seager, *J.C.S. Perkin I*, 967 (1974).

<sup>514</sup> A. S. Bailey, A. G. Holton, and J. F. Seager, *J.C.S. Perkin I*, 1003 (1972).

<sup>515</sup> A. S. Bailey and J. F. Seager, *J.C.S. Perkin I*, 763 (1974).

<sup>516</sup> A. S. Bailey and P. A. Wilkinson, *J.C.S. Perkin I*, 481 (1976).

<sup>517</sup> I. J. Tickle and C. K. Prout, *J. Chem. Soc. C*, 3401 (1971).

<sup>518</sup> A. S. Bailey, T. Morris, and Z. Rashid, *J.C.S. Perkin I*, 420 (1975).

<sup>519</sup> M. Colonna, L. Greci, and G. Padovano, *Atti Accad. Sci. Ist. Bologna, Cl. Sci. Fis., Rend.* 7, 64 (1970).

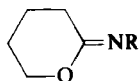
<sup>520</sup> K. A. Oglobin, V. P. Semenov, and E. V. Vassileva, *Zh. Org. Khim.* 8, 1613 (1972).

<sup>521</sup> R. A. Wohl, *Tetrahedron Lett.*, 3111 (1973).

<sup>522</sup> R. E. Harmon and D. L. Rector, *Chem. Ind. (London)*, 1264 (1965).

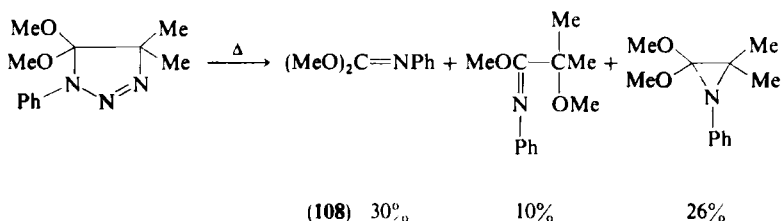
<sup>523</sup> D. L. Rector and R. E. Harmon, *J. Org. Chem.* 31, 2837 (1966).

<sup>524</sup> J. Brown and O. E. Edwards, *Can. J. Chem.* 43, 1266 (1965).



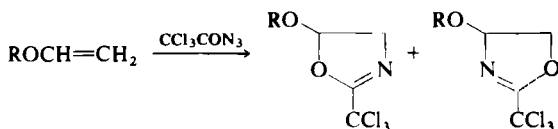
(107)

Azide addition to open-chain vinyl ethers results in different thermolysis products, depending on the azide and the enol ether employed. In Scheme 180, when  $R = \text{benzoyl}$  or ethoxycarbonyl,  $R^2 = \text{OR}^1$  and  $R^3 = \text{H}$ , imino ethers are obtained by alkoxy migration along with minor amounts of aziridine.<sup>269,525</sup> However, when  $R = \text{Ph}$  and the carbons are fully substituted, the imine (108) is obtained apparently from the reversibility of the imine-diazo compound addition (Section IV,B,2) (Scheme 181).<sup>270</sup>



SCHEME 181

Oxazolines are the principal products in the addition of acyl azides to vinyl ethers or to ketene acetals (Scheme 182).<sup>269,440</sup> Ethoxycarbonyl azide reacts



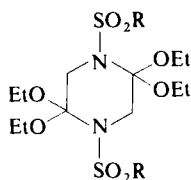
SCHEME 182

with ketene acetal to give a single oxazoline<sup>268,526</sup>; however, with phenylketene acetal (Scheme 68), the triazoline in equilibrium with the diazo compound thermolyzes to yield, in addition to the oxazoline, a mixture of triazole, imino ether, aziridine, phenyldiazomethane, and a ring-contracted imino ether.<sup>272,405</sup> Addition of sulfonyl azide to ketene acetal gives rise to piperazines (109).<sup>527</sup>

<sup>525</sup> M. L. Graziano and R. Scarpati, *Gazz. Chim. Ital.* **101**, 314 (1971).

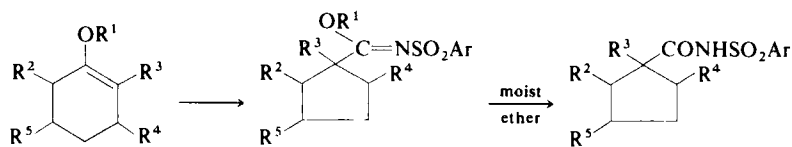
<sup>526</sup> R. Scarpati, M. L. Graziano, and R. A. Nicolaus, *Gazz. Chim. Ital.* **99**, 1339 (1969).

<sup>527</sup> G. J. Koves and I. G. Csizmadia, *Tetrahedron Lett.*, 2599 (1971).



(109)

Ring contractions are not frequent among the 5-alkoxytriazolines<sup>469,521</sup>; however, under pressure arylsulfonyl azides react with sterically congested silyl enol ethers to give clean one-carbon, ring-contracted products (Scheme 183).<sup>528</sup> For example, cyclohexanone enol ethers give cyclopentanes in 62–87% yield.

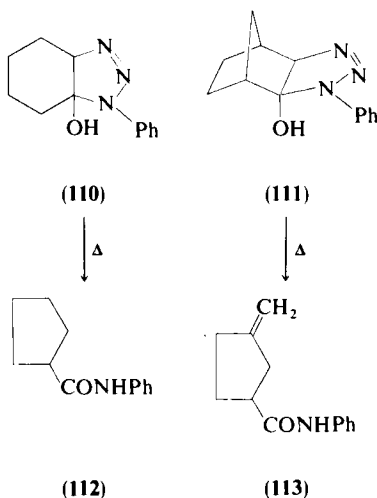


$R^1 = t\text{-butyldimethylsilyl}$

$R^2, R^3, R^4, R^5 = \text{H or Me}$

$R^2 = \beta\text{-Me}_2\text{CH}; R^3, R^5 = \text{H}; R^4 = \alpha\text{-Me}$

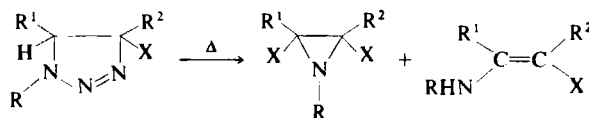
SCHEME 183



<sup>528</sup> W. G. Dauben and R. A. Bunce, *J. Org. Chem.* **47**, 5042 (1982).

5-Hydroxytriazolines generally yield triazoles by loss of water (Section IV,A,3,b). However, the fused-ring triazolines **110** and **111** when heated lead to amides **112** and **113**.<sup>260</sup> Formation of **113** involves the cleavage of the C-4/C-5 bond of the triazoline ring; both amides also result by the action of acid on the respective triazolines.

g. *Triazolines Bearing Electron-Withdrawing Substituents.* The thermolysis of triazolines bearing an electron-withdrawing substituent in the 4-position leads essentially to aziridines and enamines (Scheme 184).<sup>67,278,321,322,454</sup> The reaction is selective with *trans*-triazolines, which lead predominantly to the *trans*-aziridines.<sup>454</sup>

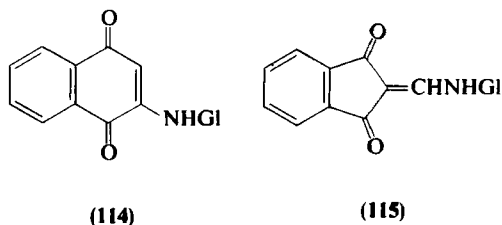


SCHEME 184

The thermolysis of ring-opened diazo compounds derived from triazoline isomerization where  $\text{R}^2 = \text{H}$  (Scheme 142) (Section IV,B,1) leads to enamines (Section IV,C,2) (Scheme 150), whereas direct thermolysis of the triazoline leads to aziridines (Scheme 162). Thus the relative amounts of aziridine and enamine will depend on the rate of isomerization of the triazoline to the diazo compound and the relative rates of thermolysis of each isomer. A high percentage of the aziridine is favored when the triazoline  $\rightleftharpoons$  diazo compound isomerization is slow; however, when significant open-ring isomer is present, enamine is the major product. For example, the thermolysis of 4-cyano-1-phenyltriazoline yields exclusively the aziridine; but the triazoline-diazo compound equilibrium mixture gives the enamine as the major thermolytic product.<sup>454</sup>

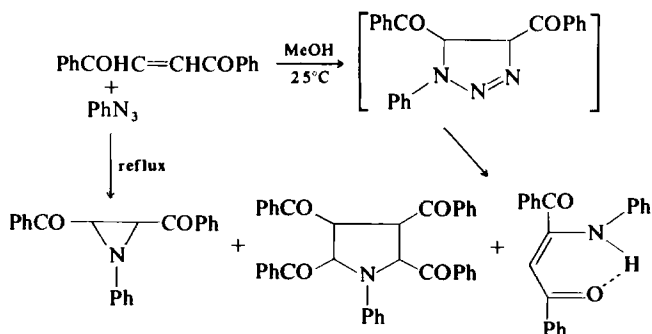
In those cases where isomerization is spontaneous, higher reaction temperatures favor aziridine formation as direct thermolysis becomes faster than the isomerization.<sup>284</sup> Enamine formation is favored by *N*-alkyl<sup>67</sup> as compared to *N*-aryl substitution<sup>278,454</sup> as also by an alkyl or aryl group in the C-5 position.<sup>284,332,454</sup> Keto groups also aid in enamine formation because they enhance the ring opening to diazo compounds (see Table I).<sup>32,284</sup> These points are illustrated by the thermolysis of the *N*-trimethylsilyltriazoline adduct from *N*-methylmaleimide, which gives 100% enamine (2-amino-*N*-methylmaleimide)<sup>310</sup> and the corresponding diaryl analog, which yields 95% aziridine.<sup>308</sup> Likewise, aziridines are obtained from fused-ring triazolines derived from phenyl azide addition to methoxycarbonylindenes and 1,2-dihydronaphthalenes.<sup>181</sup> Acyl azide addition to cyclopentadienones yield

only aziridines.<sup>529</sup> On the other hand, addition of glycosyl azide to 1,4-naphthoquinone gives, besides the triazole, two enamines (114 and 115), the ring contraction occurring via alkyl migration.<sup>317</sup>



Enamine–aziridine formation is also influenced by reaction conditions. Whereas phenyl azide addition to cinnamionitrile at 90°C results exclusively in the enamine,<sup>284</sup> thermolysis of the independently synthesized 1,5-diaryl-4-cyanotriazoline (Scheme 90) yields a mixture of the aziridine and enamine from phenyl migration.<sup>332</sup>

The enamine appears to be the only product in the reaction of phenyl azide with 1,2-dibenzoyl ethylene when it is conducted in methanol at room temperature.<sup>306</sup> However, when heated under reflux, a mixture of enamine and pyrrolidine along with minor amounts of aziridine is obtained (Scheme 185).<sup>306</sup> Hydrogen-bonding interactions are proposed as playing an important role in enamine formation.<sup>306,485</sup>

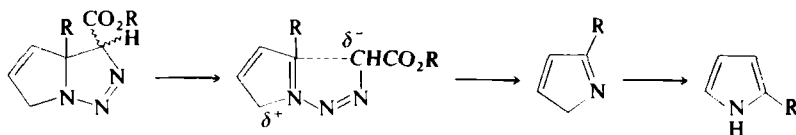


SCHEME 185

The unstable pyrrolotriazolines, derived from *cis-cis* and *trans-cis*-3-substituted 6-azidohepta-2,4-dienoate esters by intramolecular cycloaddition, decompose to 2-substituted pyrroles at rates that are both substituent and

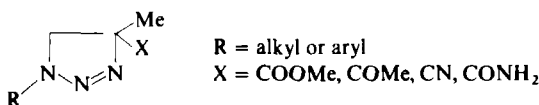
<sup>529</sup> A. Hassner, D. J. Anderson, and R. H. Reuss, *Tetrahedron Lett.*, 2463 (1977).

solvent dependent; a polar mechanism similar to a reverse Mannich reaction has been proposed (Scheme 186).<sup>302</sup>



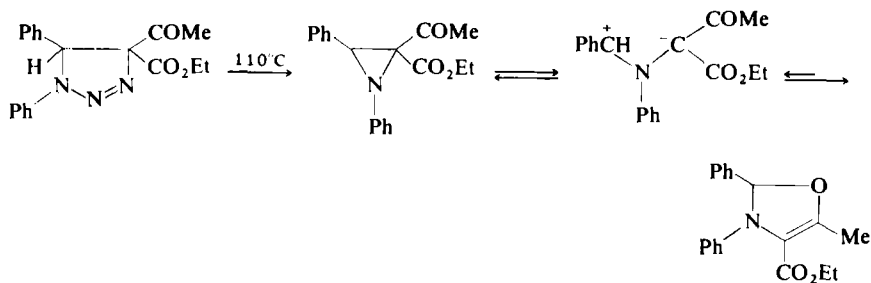
SCHEME 186

Triazolines (**116**), in which there is no free hydrogen on C-4, also thermolyze to aziridines and enamines.<sup>67,454</sup> When R is phenyl, regardless of the X substituent, aziridine is the only thermolysis product; but when R is alkyl or hetaryl,<sup>453</sup> a mixture of aziridine and enamine is obtained, the latter being the predominant product in some cases.<sup>67,453</sup> Because enamine formation from the ring-opened diazo isomers does not seem feasible, a diradical intermediate is proposed.<sup>67</sup>



(116)

Triazolines substituted with two electron-withdrawing groups in the 4-position (Scheme 83) also yield aziridines as the sole products of thermal decomposition when the 1-substituent is aryl<sup>319,321,322</sup>; when one of the electron-withdrawing substituents is an acyl group, the aziridine isomerizes spontaneously to the oxazoline via the azomethine ylide (Scheme 187).<sup>320,321,530,531</sup>

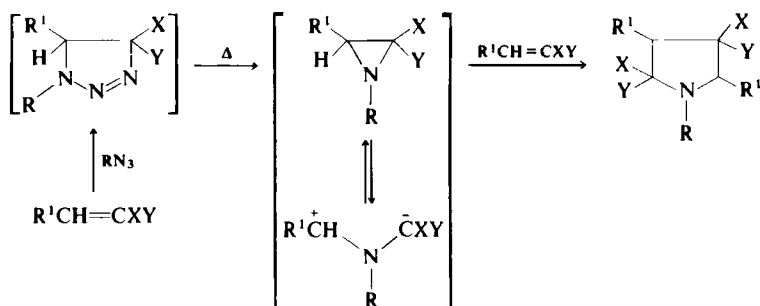


SCHEME 187

<sup>530</sup> R. Huisgen, W. Scheer, and H. Huber, *J. Am. Chem. Soc.* **89**, 1763 (1967).

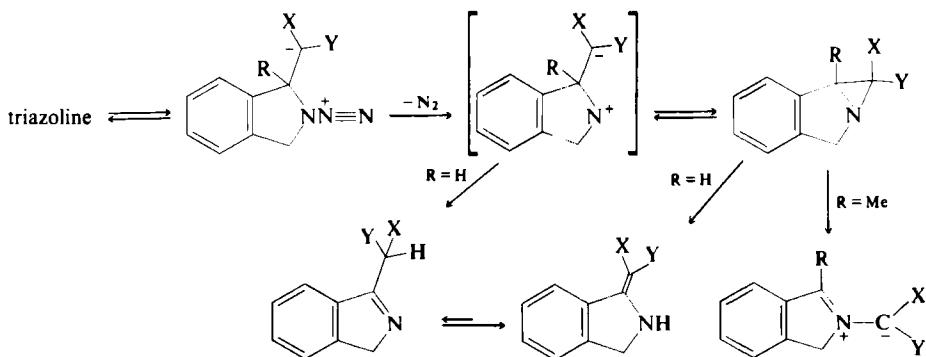
<sup>531</sup> J. W. Lown, *Rec. Chem. Prog.* **32**, 51 (1971).

With nitrile as one of the electron-withdrawing groups, the triazoline decomposes *in situ* to an aziridine that exists in equilibrium with the corresponding azomethine ylide; the latter reacts with a molecule of the olefinic reagent and gives rise to a pyrrolidine (Scheme 188).<sup>319,322</sup>



SCHEME 188

The isoindolotriazolines (Scheme 86) are exceptions; when X and/or Y = CN, a mixture of an exocyclic enamine and an isoindolenium methylide is formed via a zwitterionic intermediate, which is proposed to involve a C—N rather than an N—N bond cleavage of the triazoline ring (Scheme 189).<sup>324</sup>



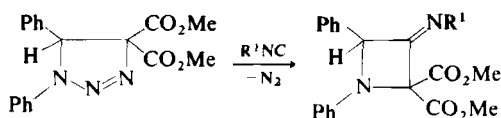
SCHEME 189

Triazolines bearing two ester groups on C-4, when thermolyzed in the presence of different dipolarophiles, such as alkenes, alkynes, aldehydes, imines, and ketenes, yield pyrrolidines,<sup>532</sup> pyrrolines,<sup>533</sup> oxazolidines, and

<sup>532</sup> F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 2373 (1972); 310 (1974).

<sup>533</sup> F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 2381 (1972).

imidazolidines.<sup>534</sup> Thermolysis in the presence of isonitrile leads to imino-azetidines (Scheme 190).<sup>535</sup>



SCHEME 190

Triazolines bearing three electron-withdrawing groups (Scheme 85) undergo complex thermolysis reactions. Aziridine formation is observed but sometimes the azide cycloreversion operates; pyrrolidines are thus formed by reaction of the olefins with the azomethine ylides from the aziridines. The aziridines also dimerize to piperazines under the conditions of thermolysis.<sup>446</sup>

Triazolines with an electron-withdrawing substituent in the 5-position are rare; they are obtained as secondary products in the nonregioselective addition of azides to methacrylic derivatives (Scheme 75). Their thermolysis is similar to that of the 4-isomers; a mixture of aziridine and enamine is formed.<sup>67</sup>

The 5-benzoyltriazoline (Scheme 76) upon heating gives aziridine although it enters into competition with the retroaddition reaction, forming the starting azide and olefin.<sup>292</sup>

Triazolines resulting from diazomethane addition to the carbon–nitrogen double bond in oximes decompose rapidly even at 20°C to give *N*-alkoxyaziridines.<sup>361,362</sup>

#### ACKNOWLEDGMENTS

P. K. K. thanks Mr. Terrance Tita for assistance in the preparation of the manuscript, Mrs. T. Hudeček and Mrs. M. Kastelic for drawing formulas and schemes, Miss Lini S. Kadaba for proofreading, and the NINCDS, NIH, for research grant 1 R01 NS 16843.

<sup>534</sup> F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 3437 (1973); *Chem. Commun.*, 199 (1972).

<sup>535</sup> K. Burger, F. Manz, and A. Braun, *Synthesis*, 250 (1975).



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**$\Delta^3$ - and  $\Delta^4$ -1,2,3-Triazolines**

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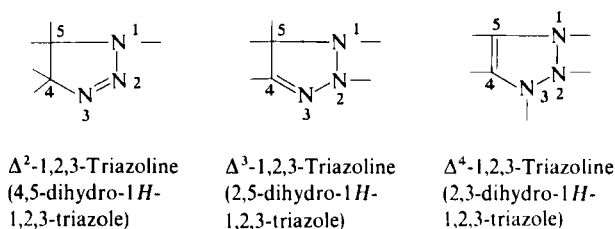
**I. Introduction**

Most known 1,2,3-triazoline chemistry is of the  $\Delta^2$ -compounds<sup>1</sup>; few studies concern the  $\Delta^3$ - and  $\Delta^4$ -compounds. In 1959, Mohr and Hertel first described several  $\Delta^4$ -1,2,3-triazoline intermediates.<sup>2</sup> Despite a previous assignment of a  $\Delta^4$ -triazoline structure for the phenyl azide-acrylonitrile

<sup>1</sup> P. K. Kadaba, B. Stanovnik, and M. Tišler, this volume, p. 217.<sup>2</sup> R. Mohr and H. Hertel, Ger. Patent 1,061,789 (1959) [CA 55, P10472-3h (1961)].

adduct,<sup>3</sup> later work established the product as a 1-phenyl-4-cyano- $\Delta^2$ -1,2,3-triazoline.<sup>4</sup> Procedures for the synthesis of the  $\Delta^3$ - and  $\Delta^4$ -compounds are limited in scope. There are no previous reviews on the chemistry of  $\Delta^3$ - and  $\Delta^4$ -1,2,3-triazolines.

**Nomenclature.** The three forms of the 1,2,3-triazoline ring system along with their *Chemical Abstracts* naming are presented in Scheme 1.



SCHEME 1

## II. Synthesis of the $\Delta^3$ - and $\Delta^4$ -Triazoline Ring Systems

About a half-dozen cases are recorded on the formation of  $\Delta^3$ -triazolines; the sodium borohydride reduction of triazolium compounds<sup>5</sup> and the vinyl azide additions to triazolinediones<sup>6</sup> appear most promising for extended application. Only three synthetic approaches exist for the  $\Delta^4$ -compounds, of which the route employed by Mohr and Hertel<sup>2,2a</sup> has greater general applicability.

Besides starting from the triazole ring skeleton itself,<sup>5</sup> the synthesis of the  $\Delta^3$ - and  $\Delta^4$ -1,2,3-triazolines may be envisaged as union of the N–N and C–C–N or, alternatively, the C–C and N–N–N fragments. Vinyl azide addition to triazolinediones,<sup>6</sup> the cyclization of desylamine hydrazones (Section II,A,5), and the reaction of diazonium salts of primary amines with inorganic esters of diethanolamines (Section II,B,1) may be considered to fall into the first category; of the remaining, the reactions of diazoaminobenzene and azimine with acetylenedicarboxylic esters (Sections II,B,2 and 3) come under the second approach.

<sup>2a</sup> R. Mohr and H. Hertel, Ger. Patent 1,075,623 (1960) [CA 56, P3484g (1962)].

<sup>3</sup> S. M. Gurvich and A. P. Terentev, *Sb. Stat. Obshch. Khim. Akad. Nauk. SSSR* 1, 409 (1953) [CA 49, 1047 (1955)].

<sup>4</sup> R. Huisgen, G. Szeimies, and L. Mobius, *Chem. Ber.* 99, 475 (1966).

<sup>5</sup> T. Isida, T. Akiyama, N. Mihara, S. Kozima, and K. Sisido, *Bull. Chem. Soc. Jpn.* 46, 1250 (1973).

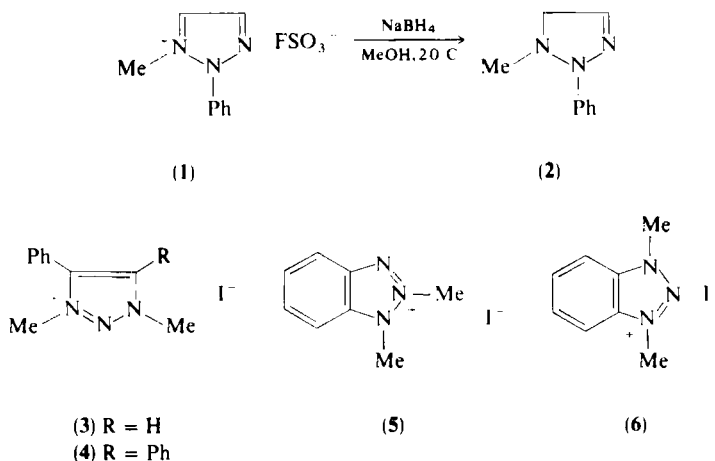
<sup>6</sup> A. Hassner, D. Tang, and J. Keogh, *J. Org. Chem.* 41, 2102 (1976).

A. SYNTHESIS OF  $\Delta^3$ -1,2,3-TRIAZOLINES

## 1. Sodium Borohydride Reduction of Triazolium Fluorosulfonates

Sodium borohydride reduction of 1,2-disubstituted-1,2,3-triazolium fluorosulfonate (**1**) gives the  $\Delta^3$ -1,2,3-triazoline **2** in 92% yield; however, neither the 1,3,4- and 1,3,4,5-substituted 1,2,3-triazolium iodides (**3** and **4**) nor the 1,2- and 1,3-dimethylbenzotriazolium iodides (**5** and **6**) are reduced.<sup>5</sup>

Sodium borohydride reacts selectively at the immonium moiety<sup>7-9</sup> in the azolium salts; reduction occurs depending on the substitution pattern and the formation of the immonium ion system.<sup>5</sup>



## 2. 1,3-Addition of Vinyl Azides to Triazolinediones

4-Phenyl-1,2,4-triazoline-3,5-dione<sup>10</sup> undergoes 1,3-cycloaddition at room temperature across the N–N double bond with vinyl azides to form bicyclic  $\Delta^3$ -1,2,3-triazolines (Scheme 2) (Table I)<sup>6</sup>; the relative rates of addition of

<sup>7</sup> R. E. Lyle, D. A. Nelson, and P. S. Anderson, *Tetrahedron Lett.*, 553 (1962); P. S. Anderson and R. E. Lyle, *ibid.*, 153 (1964); R. E. Lyle and P. S. Anderson, *Adv. Heterocycl. Chem.* **6**, 45 (1966).

<sup>8</sup> G. M. Clarke and P. Sykes, *Chem. Commun.*, p. 370 (1965).

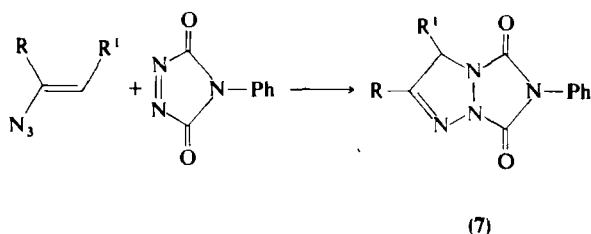
<sup>9</sup> P. K. Kadaba, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.* **13**, 835 (1976); *Tetrahedron Lett.*, 3715 (1974).

<sup>10</sup> R. A. Clement, *J. Org. Chem.* **25**, 1724 (1960); **27**, 1115 (1962); D. H. R. Barton, T. Shioiri, and D. A. Widdowson, *Chem. Commun.*, 939 (1970); W. Ried and S. H. Lim, *Justus Liebigs Ann. Chem.*, 129 (1973); D. J. Pasto and J. K. Barchardt, *J. Am. Chem. Soc.* **96**, 6944 (1974); D. J. Pasto and A. F. T. Chen, *Tetrahedron Lett.*, 2955 (1972).

TABLE I  
 $\Delta^3$ -TRIAZOLINES (7A-7E) PREPARED FROM  
 VINYL AZIDES (A-E) AND TRIAZOLINEDIONE

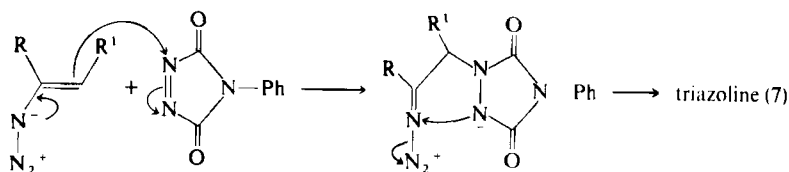
Vinyl azide	R	R <sup>1</sup>	Yield (%) (7A-7E)
<b>A</b>	Ph	H	72
<b>B</b>	Ph	CH <sub>3</sub>	73
<b>C</b>	H	<i>t</i> -Bu	55
<b>D</b>	<i>p</i> -MeOPh	H	78
<b>E</b>	<i>p</i> -NO <sub>2</sub> Ph	H	No reaction

substituted vinyl azides indicate that electron-donating substituents favor addition.



SCHEME 2

A reaction mechanism in which the  $\beta$  carbon of the vinyl azide attacks the N-N double bond of the triazolidione to give an intermediate which cyclizes with loss of nitrogen to the triazoline has been proposed (Scheme 3).<sup>6</sup>



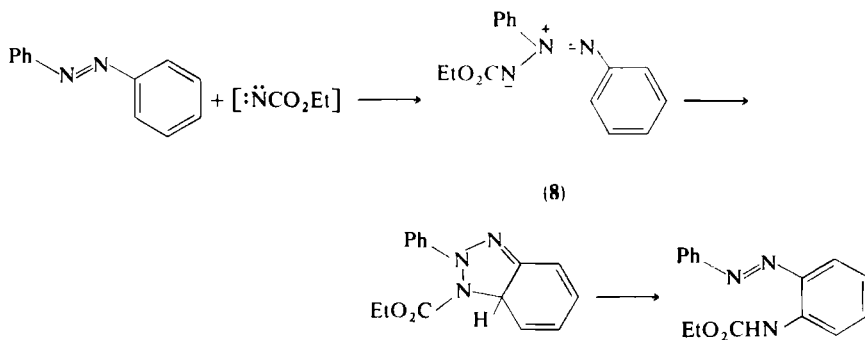
SCHEME 3

The observations that azide **A** reacts twice as fast as **B**, which in turn reacts faster than **C**, are consistent with the proposed mechanism, and may be attributed to steric factors ( $R^1 = \text{H}, \text{CH}_3$ , or *t*-Bu). Similarly, the much faster reaction of **D** over **A** and the failure of **E** to undergo addition have also been rationalized on the basis of the changing nucleophilicity at the  $\beta$  carbon as influenced by resonance contributions from the para substituents of the phenyl group in the  $\alpha$  position.<sup>6</sup> The reaction mechanism is analogous to the

reactions of vinyl azides with bromine<sup>11</sup> and ketenes,<sup>12</sup> both of which are postulated to involve an initial attack by the  $\beta$  carbon on the electrophile; it is unlike that which operates in vinyl azide additions to acetylenic<sup>13</sup> and olefinic bonds,<sup>14-17</sup> where addition occurs across the termini of the azide function.

### 3. Reaction of Nitrenes with Azo Compounds

The thermolysis of ethyl azidoformate in excess azobenzene at 115–117°C gives, as the major product, ethyl 2-(phenylazo)carbanilate; the proposed reaction mechanism suggests the formation of an azimine (8) (by attack of the nitrene on the azo group) which rearranges to the carbanilate via a bicyclic  $\Delta^3$ -triazoline ring system,<sup>18</sup> apparently formed by a 1,5-electrocyclization<sup>19</sup> of 8 (Scheme 4).



SCHEME 4

### 4. Action of Isocyanate on Aminotriazole

5-Amino-1-benzyl-4-carbethoxy-1*H*-1,2,3-triazole with methyl isocyanate in the presence of triethylamine yields the 5-methylcarbamoylimino substituted  $\Delta^3$ -triazoline (9) (Scheme 5).<sup>20</sup>

<sup>11</sup> A. Hassner and A. B. Levy, *J. Am. Chem. Soc.* **92**, 1672 (1970).

<sup>12</sup> A. Hassner and A. S. Miller, *J. Org. Chem.* **37**, 2682 (1972).

<sup>13</sup> G. L'abbe, *Chem. Rev.* **69**, 345 (1969); T. L. Gilchrist and G. E. Gymer, *Adv. Heterocycl. Chem.* **16**, 33 (1974).

<sup>14</sup> A. Padwa, A. Ku, H. Ku, and A. Mazzu, *Tetrahedron Lett.*, 551 (1977).

<sup>15</sup> A. Padwa, A. Ku, H. Ku, and A. Mazzu, *J. Org. Chem.* **43**, 66 (1978); A. Padwa, H. Ku, and A. Mazzu, *J. Org. Chem.* **43**, 381 (1978).

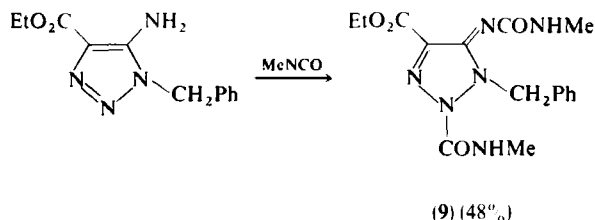
<sup>16</sup> J. H. Boyer, W. E. Krueger, and R. Modler, *Tetrahedron Lett.*, 5979 (1968).

<sup>17</sup> G. L'abbe, *Angew. Chem. Int. Ed. Engl.* **14**, 775 (1975).

<sup>18</sup> R. C. Kerber and P. J. Heffron, *J. Org. Chem.* **37**, 1592 (1972).

<sup>19</sup> E. C. Taylor and I. J. Turchi, *Chem. Rev.* **79**, 181 (1979).

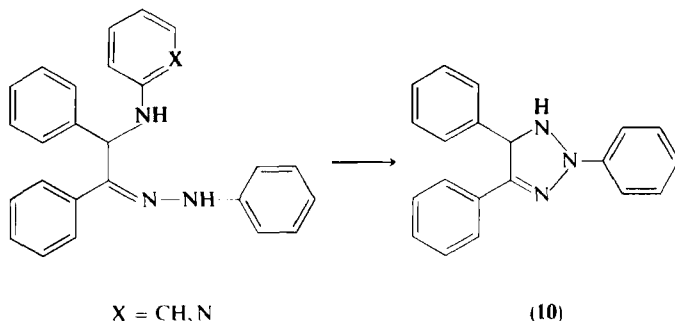
<sup>20</sup> L. Capuano, M. Welter, and R. Zander, *Chem. Ber.* **102**, 3698 (1969).



SCHEME 5

### 5. Reaction of Desylamines with Phenylhydrazine

Phenyldesylamine,<sup>21</sup> when heated under reflux with phenylhydrazine in acetic acid, forms the 2,4,5-triphenyl-2,5-dihydro-1*H*-1,2,3-triazole **10** (Scheme 6).<sup>22</sup> The 2-pyridyldesylamine<sup>21</sup> leads to the same triazoline (**10**), with the pyridine fragment being lost during the cyclization in place of the benzene.<sup>22</sup>



SCHEME 6

## B. SYNTHESIS OF $\Delta^4$ -1,2,3-TRIAZOLINES

### 1. From Diazonium Salts of Primary Amines and Inorganic Acid Esters of Diethanolamines

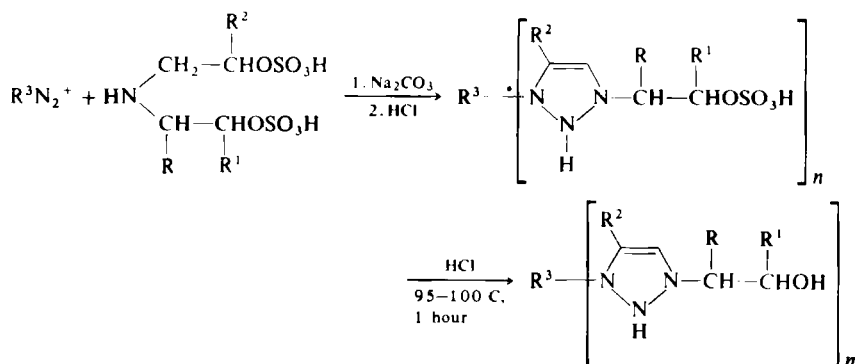
The preparation of  $\Delta^4$ -1,2,3-triazolines (Scheme 7, where  $n = 1$  or  $2$ )<sup>2,2a</sup> involves the reaction of diazonium compounds of primary aromatic or

<sup>21</sup> I. A. Kaye, C. L. Parris, and W. J. Burlant, *J. Am. Chem. Soc.* **75**, 746 (1953); K. Voigt, *J. Prakt. Chem.* **34**, 2 (1886).

<sup>22</sup> A. Lespagnol, J.-P. Henichart, R. Houssin, and B. Lablanche, *Bull. Soc. Chim. Fr.*, 1891 (1974).

heterocyclic mono- or diamines at pH 8–12 with inorganic acid esters of diethanolamines.<sup>2</sup> When dialkylamines are used in place of the esters, 1-alkyl- $\Delta^4$ -triazolines are obtained.<sup>2a</sup> Numerous examples are known of both groups of  $\Delta^4$ -triazolines derived from aromatic or heterocyclic primary amines.<sup>2,2a</sup> Most of the triazoline-1-ethanesulfonic acids melt at high temperatures (> 200°C), while the 1-alkyltriazolines melt at lower temperatures.

The triazoline-1-ethanesulfonic acid esters may be hydrolyzed to the corresponding alcohols in aqueous acid (Scheme 7).<sup>2a</sup>



SCHEME 7.  $n = 1$ ;  $R = R^1 = H$ , Me, or Et;  $R^2 = H$  or Me;  $R^3 = Ph$ ; 2-, 3-, or 4-ClPh; 2-, 3-, or 4-MePh; 3-BrPh; 4-EtPh; 3-PhSO<sub>3</sub>H; 3-NO<sub>2</sub>Ph; 2- or 4-MeOPh; 3-EtO<sub>2</sub>CPh; 2,4-Me<sub>2</sub>Ph or 2,4-(MeO)<sub>2</sub>Ph; 2,5-(EtO)<sub>2</sub>Ph; 2,5-Cl<sub>2</sub>Ph; 2,5-Cl(CF<sub>3</sub>)Ph; 3,5-Cl(PhO)Ph; 2,5-Cl(MeO)Ph; 2,5-MeNO<sub>2</sub>Ph; 2,6-MeClPh; 2,5-Me(MeO)Ph; 2,5-(MeO)(EtSO<sub>2</sub>)Ph; 2,5-(MeO)(EtNSO<sub>2</sub>)Ph; 2,5-(MeO)(CONH<sub>2</sub>)Ph; 2,4,6-Me<sub>3</sub>Ph; 4-Ph-Ph; 2-MeO-3-dibenzofuran-3-yl; 3-Chlorobenzopyrazol-6-yl; 4-AcNHPh; 3,4-(AcNH)(MeO)Ph; 1-Naphthyl; and when  $n = 2$ ,  $R^3 = 4,4'$ -Biphenylene; 2,2'-Dimethoxybiphenylene; (2-NaO<sub>3</sub>SPhCH=)<sub>2</sub>.

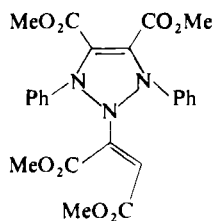
## 2. From Diazoaminobenzene and Dimethyl Acetylenedicarboxylate

Reaction of diazoaminobenzene with two molecules of dimethyl acetylenedicarboxylate yields 7% of the  $\Delta^4$ -1,2,3-triazoline compound **11** along with 10% of the expected succinate (**12**) and a trace of the fumarate (**13**).<sup>23</sup> The 1:1 and the 1:2 adducts, **13** and **12**, respectively, are postulated to be formed in a Michael-type addition similar to that which occurs with heterocyclic compounds possessing NH groups, when treated with dimethyl acetylenedicar-

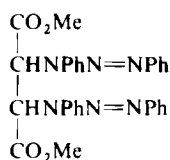
<sup>23</sup> R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C*, 389 (1968).



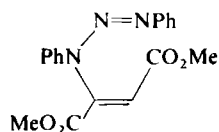
boxylate.<sup>24,25</sup> Triazoline **11** was recovered unchanged from refluxing acetic anhydride, thus indicating the absence of an NH group.



(11)



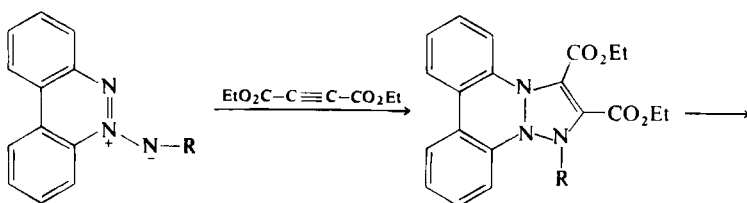
(12)



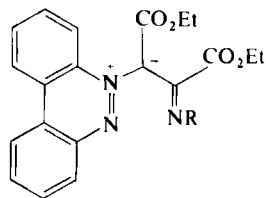
(13)

### 3. 1,3-Dipolar Cycloaddition of Azimine with Acetylenedicarboxylic Esters

The three-nitrogen azimine 1,3-dipolar system in benzocinnolinium ylides<sup>26</sup> undergoes cycloaddition with acetylenedicarboxylic esters to give azomethineimines, presumably derived from the initial  $\Delta^4$ -triazoline 1,3-cycloadduct by an electrocyclic ring opening (Scheme 8).<sup>27</sup>



R = CO<sub>2</sub>Et or COPh



SCHEME 8

<sup>24</sup> R. M. Acheson, *Adv. Heterocycl. Chem.* **1**, 125 (1963).

<sup>25</sup> R. M. Acheson, M. W. Foxton, K. J. Mills, and P. J. Abbott, *J. Chem. Soc. C*, 882 (1967).

<sup>26</sup> S. F. Gait, C. W. Rees, and R. C. Storr, *Chem. Commun.*, 1545 (1971).

<sup>27</sup> S. F. Gait, M. J. Rance, C. W. Rees, and R. C. Storr, *Chem. Commun.*, 688 (1972).

### III. Structure and Physical Properties

#### A. STRUCTURE

Both  $\Delta^3$ - and  $\Delta^4$ -1,2,3-triazolines have the 1*H*-structure, although  $\Delta^3$ -triazolines may be considered as the 1,5-dihydro derivatives of 2*H*-1,2,3-triazoles<sup>22</sup>; the parent compound of neither triazoline is known.

#### B. SPECTROSCOPIC PROPERTIES

##### 1. Ultraviolet Spectra

The ultraviolet spectrum of  $\Delta^4$ -1,2,3-triazoline-4,5-dicarboxylate (**11**) has been recorded.<sup>23</sup>

##### 2. Infrared Spectra

The infrared spectrum has been employed mainly to establish the presence<sup>22</sup> or absence<sup>23</sup> of the NH function in the  $\Delta^3$ - and  $\Delta^4$ -triazolines; in **10** the NH absorption appears at  $3300\text{ cm}^{-1}$ .<sup>22</sup> Absence of imine–enamine tautomerization in **7** is also established by IR.<sup>6</sup>

##### 3. Mass Spectra

Unlike the labile  $\Delta^2$ -1,2,3-triazolines,  $\Delta^3$ - and  $\Delta^4$ -triazolines do not suffer nitrogen loss in the mass spectrum, and molecular ion peaks have been reported for several related bicyclic  $\Delta^3$ -1,2,3-triazolines.<sup>6</sup>

##### 4. Nuclear Magnetic Resonance Spectra

The structural assignments of the  $\Delta^3$ - and  $\Delta^4$ -1,2,3-triazolines are based largely on their proton NMR spectra, measured in deuteriochloroform.<sup>5,6,20,23</sup> The two hydrogen atoms at C-5 in the  $\Delta^3$ -triazolines **2**<sup>5</sup> and in **7A** and **7D**<sup>6</sup> appear as a singlet in the region  $\delta$  3.76–4.92 ppm, although in **2** the 4-position is unsubstituted. On the other hand, the C-5 proton in **7C** gives a doublet ( $J = 1.5\text{ Hz}$ ) at  $\delta$  4.78 ppm, and that of **7B** bearing a 5-methyl substituent (doublet at  $\delta$  1.62 ppm;  $J = 6.5\text{ Hz}$ ) appears as a quartet at  $\delta$

5.65 ppm ( $J = 6.5$  Hz).<sup>6</sup> 1-Alkyl substitution moves the chemical shifts to slightly higher field in **2**,<sup>5</sup> as compared to **7**, which has an electron-withdrawing group at N-1.<sup>6</sup>

The CH protons in the 4-position of both **2** and **7C** shift to very low field; they appear along with the phenyl proton multiplets in the region  $\delta$  6.7–7.53 ppm. Likewise, the 4-phenyl protons in **7A** and **7B** lie in the same range as the N-phenyl protons, and multiplets at  $\delta$  7.3–7.93 ppm are obtained.

The assignment of structure **9** is based solely on the NMR spectrum, CH<sub>3</sub> (triplet,  $\delta$  1.23), CH<sub>2</sub> (quartet,  $\delta$  4.20); CH<sub>2</sub> (singlet,  $\delta$  5.36), Ph, 2NH (multiplet,  $\delta$  7.37), and 2CH<sub>3</sub> (doublet,  $\delta$  2.74,  $J = 4.5$  Hz).<sup>20</sup>

The  $\Delta^4$ -triazoline **11** showed a single proton at higher field than for diethyl maleate, indicating that the ester groups might be cis, an arrangement which would reduce steric congestion.<sup>23</sup> Other possible structures for **11** were excluded based on the absence of NH, as shown by the NMR spectrum which was unaltered by addition of deuterium oxide.<sup>23</sup>

### C. OTHER PHYSICAL PROPERTIES

#### *Refractive Index*

The refractive index of 1-methyl-2-phenyl- $\Delta^3$ -1,2,3-triazoline (**2**), which is obtained as a viscous liquid, has been measured ( $n_{26}^D = 1.5738$ ).<sup>5</sup>

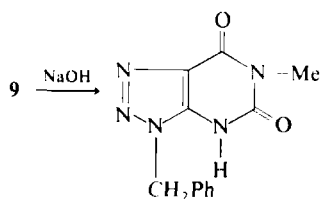
### IV. Reactions of $\Delta^3$ - and $\Delta^4$ -1,2,3-Triazolines

The chemistry of  $\Delta^3$ - and  $\Delta^4$ -1,2,3-triazolines is still in its beginnings and few reactions have been reported.

The  $\Delta^4$ -triazolines, unlike the  $\Delta^2$ -compounds, are stable toward acids, and the hydrochlorides of  $\Delta^4$ -triazoline-1-ethanols have been obtained by heating the corresponding 1-ethanesulfonic acids with hydrochloric acid (Scheme 7).<sup>2a</sup> Similarly, the  $\Delta^4$ -triazoline **11** remains stable in refluxing acetic anhydride.<sup>23</sup>

On the other hand, an electron-withdrawing substituent on N-1 appears to induce ring opening by N–N bond fission, as, for example, in the 1-ethoxycarbonyl substituted  $\Delta^3$ -triazoline in Scheme 4<sup>18</sup> and the  $\Delta^4$ -triazoline adduct in Scheme 8.<sup>27</sup>

The  $\Delta^3$ -triazoline **9** (Scheme 5) undergoes cyclization quantitatively to a fused pyrimidine ring system<sup>28</sup> under the action of aqueous sodium hydroxide (Scheme 9).<sup>20</sup>



SCHEME 9

## ACKNOWLEDGMENTS

The author thanks Professors M. Tišler and B. Stanovnik for reviewing the manuscript. The author is grateful to the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, for the award of research grant 5R01 NS 16843 03.

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